

# **APPROACH TO BLEEDING DISORDERS**

**BY:**

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# LEARNING OBJECTIVES

- To know the function of platelets and the relationship between the platelet count in peripheral blood and the extent of abnormal bleeding.
- To know about the diseases associated with
  - 1) a failure of platelet production
  - 2) a shortened platelet lifespan, especially immune thrombocytopenic purpura (ITP).
- To know the principles of investigation of patient suspected of having a haemostatic defect.

*cont'd...*

- To understand the role of platelets, blood vessel wall and coagulation factors in normal haemostasis.
- To know the classification of haemostatic defects.
- To know the platelet morphology and life span.
- To know the platelet function and diseases due to platelet function disorders.
- To know the causes of thrombocytopenic purpura and non-thrombocytopenic purpura.

# Investigations of Bleeding Disorders

## Clinical Features:

- ❖ Complaints
- ❖ Full Clinical Examinations
- ❖ History of Bleeding
- ❖ Family History of Bleeding
- ❖ If bleeding present, what is the pattern of bleeding episodes



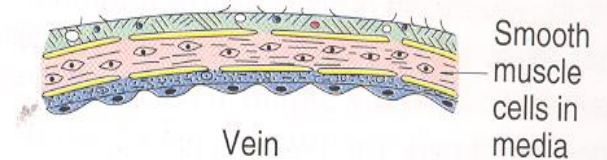
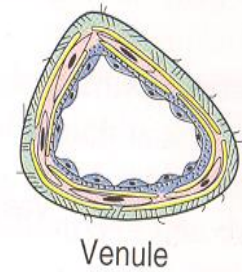
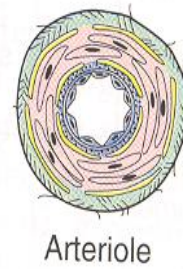
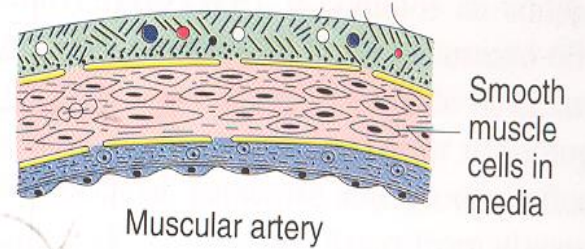
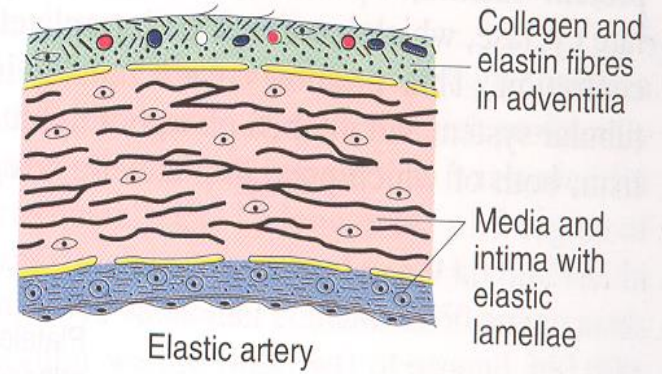
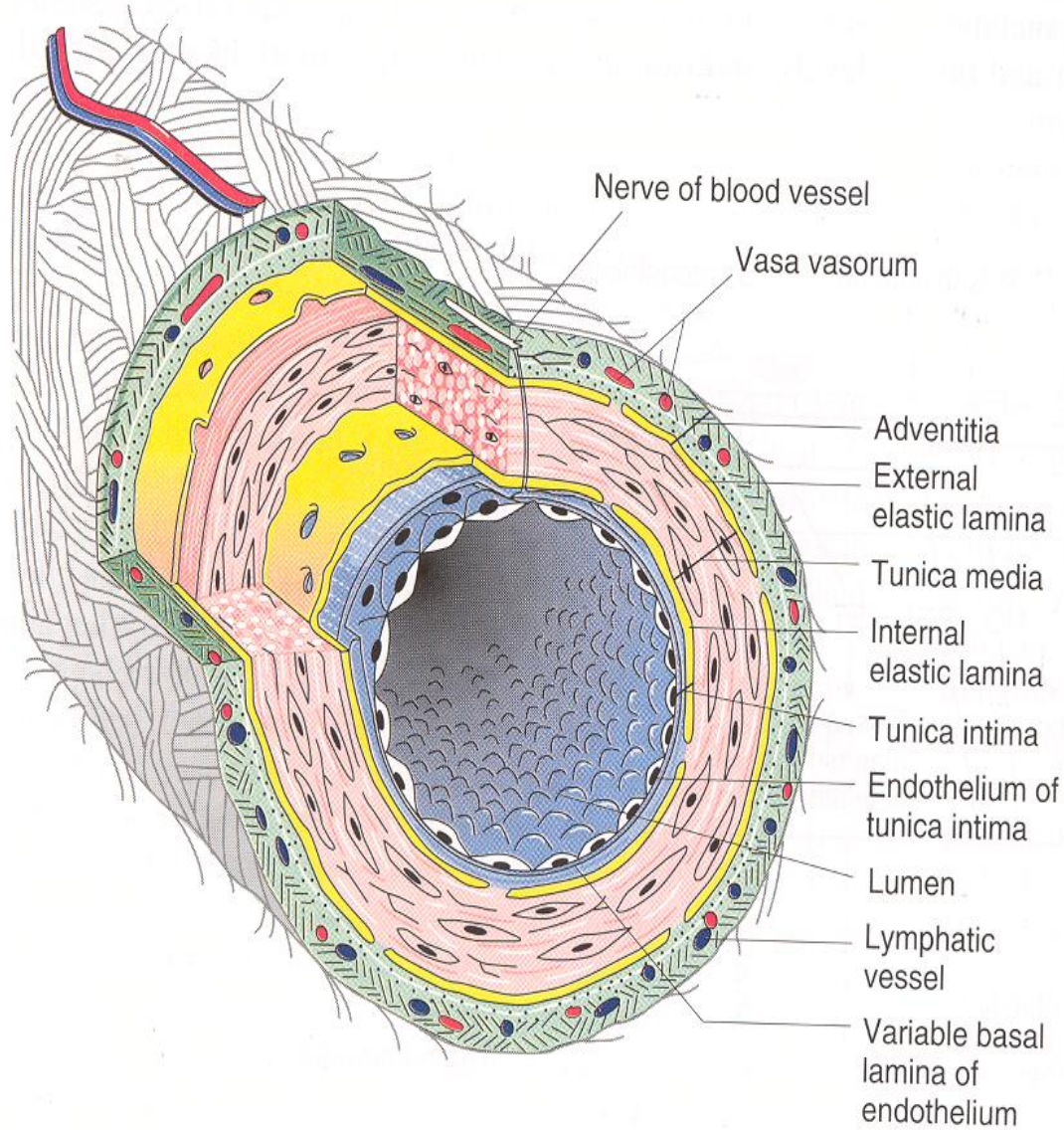
**Clinical distinction can frequently be made between bleeding due to platelet defects and (in number or function) and clotting defects (coagulation defects) .**

- a. Patient with platelets defects or blood vessel wall defects usually present with superficial bleeding into the skin (purpura) and from epithelial surfaces of organs. This is called (mucocutaneous bleeding).
- b. Patients with clotting defects (coagulation factors deficiencies) usually present with bleeding into deep tissue and muscles (haematomas) and joints (haemarthrosis) this is called musculoskeletal bleeding.

# NORMAL HAEMOSTASIS:

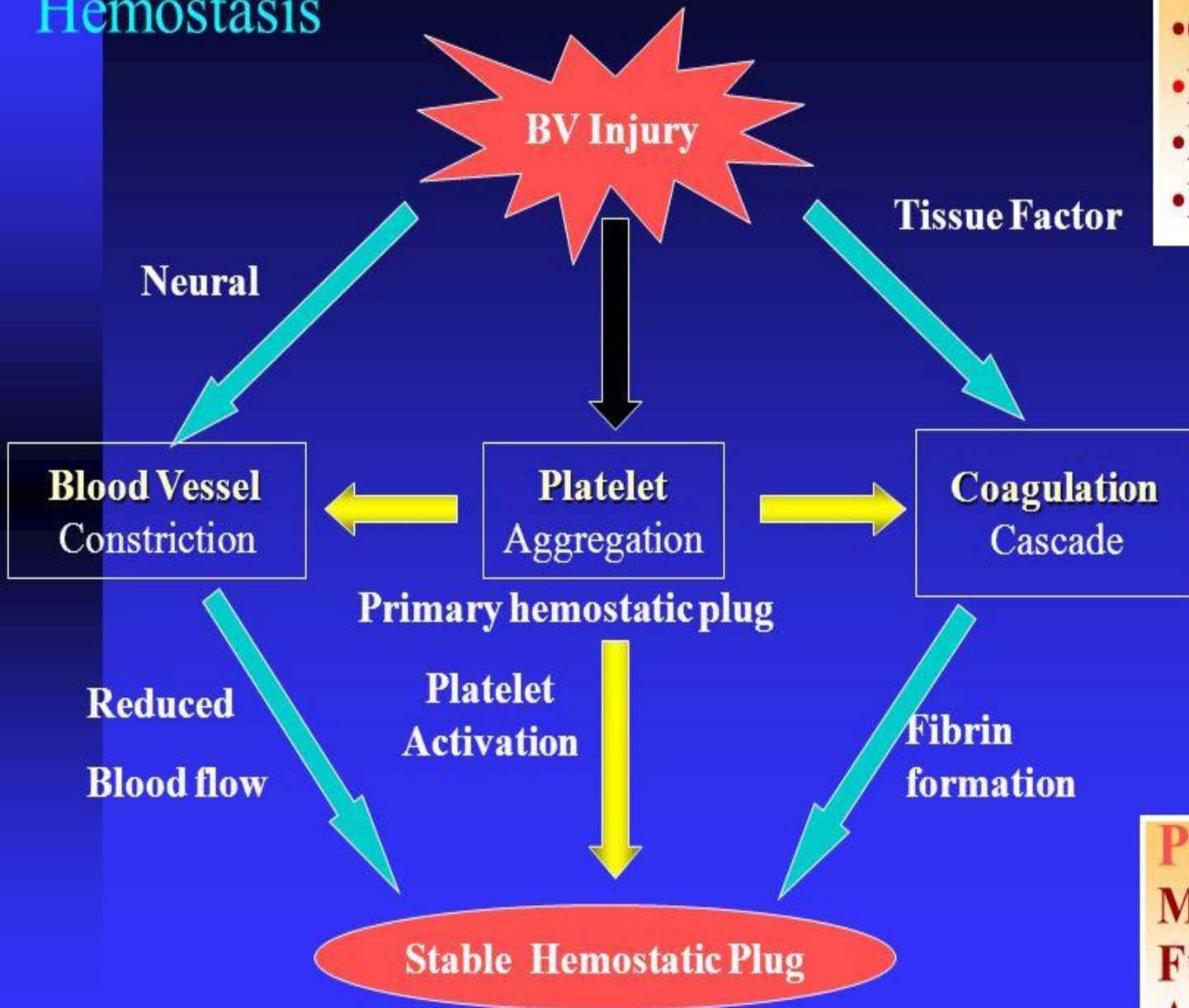
The cessation of bleeding following trauma to blood vessel is result from three processes:

- 1.) The contractions of vessel walls.
- 2.) The formation of the platelets plug at the site of the break in the vessel wall.
- 3.) The formation of a fibrin clot within and around the platelet aggregates.





# Hemostasis

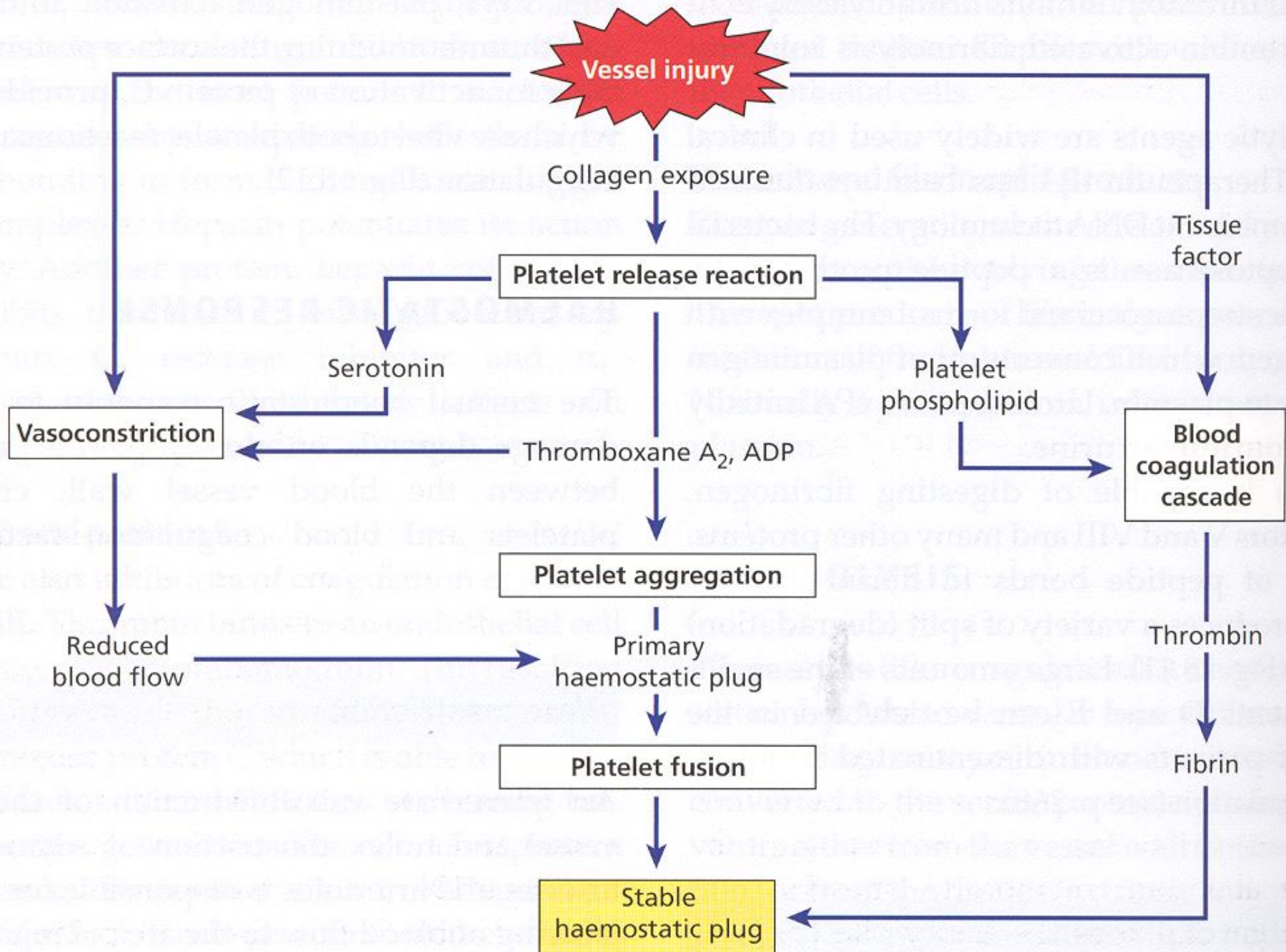


## Lab Tests

- CBC-Plt
- BT,(CT)
- PT
- PTT

## Plt Study

- Morphology
- Function
- Antibody







**Early platelet fibrin hemostatic plug.**





**Late platelet fibrin hemostatic plug.**

# Classification of haemostatic defects

The action of platelets and the clotting mechanism are closely intertwined in the prevention of bleeding. However, bleeding arise from defects in one of the three processes:

- 1) Thrombocytopenia (a low platelet count) (the commonest cause).
- 2) Abnormal platelet function.
- 3) A defect in the clotting mechanism (the second commonest cause).

Patients with clotting defects usually present with bleeding into deep tissues; that is, muscles or joints. Patients with a deficiency of platelets usually present with mucocutaneous bleeding; that is, bleeding into the skin and from the epithelial surfaces of the nose, uterus and other organs.



*cont'd...*

Petechial haemorrhages and ecchymoses and bleeding from other sites may occur when the number of platelets falls below  $50 \times 10^9/L$ . At levels between 20 and  $50 \times 10^9/L$ , petechiae, ecchymoses and nose bleeds are the commonest symptoms, but below  $20 \times 10^9/L$ , gross haemorrhage (melaena, haematemesis, haematuria) becomes increasingly common.



**Multiple pin-point haemorrhages (petechiae) on the legs of a patient with idiopathic thrombocytopenic purpura (ITP).**



**Large ecchymoses on both the upper arms of a woman with ITP.**

# Hereditary Vascular Disorders

- \* Hereditary Haemorrhagic Telangiectasia (Rendu-weber-osler syndrome)
- \* Kasabach-merritt syndrome (Haemangioma – Thrombocytopenia)
- \* Ehlers-Danlos syndrome
- \* Pseudoxanthoma elasticum
- \* Homocystinuria
- \* Marfan syndrome
- Osteogenesis imperfecta



# Hereditary Haemorrhagic Telangiectasia





Ehlers-Danlos syndrome

# Acquired Vascular Disorders

- \* Allergic purpura (Henoch-Schonlein purpura)
- \* Paraproteinemia and amyloidosis.
- \* Senile purpura
- \* Drug-induced vascular purpuras (Steroid therapy, sulfonamides, iodides, aspirin, digoxin, methyldopa, estrogen, allopurinol, penicillin and other antibiotics).
- \* Vitamin C Deficiency (Scurvy)
- \* Purpura simplex (Easy bruisability)
- \* Psychogenic purpura
- \* Purpura associated with infections.





Allergic purpura (Henoch-Schonlein purpura)





Paraproteinemia and amyloidosis





Senile purpura

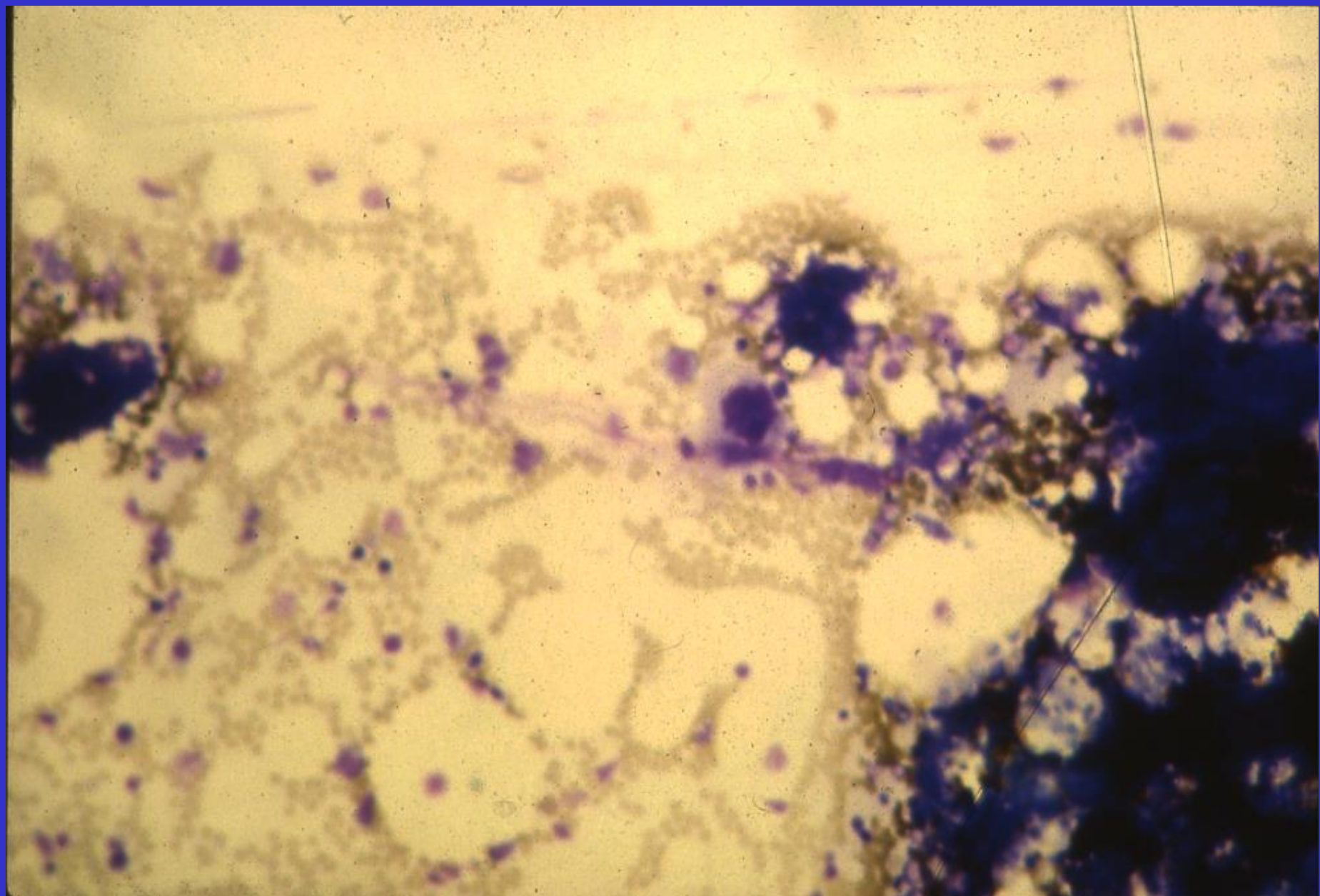




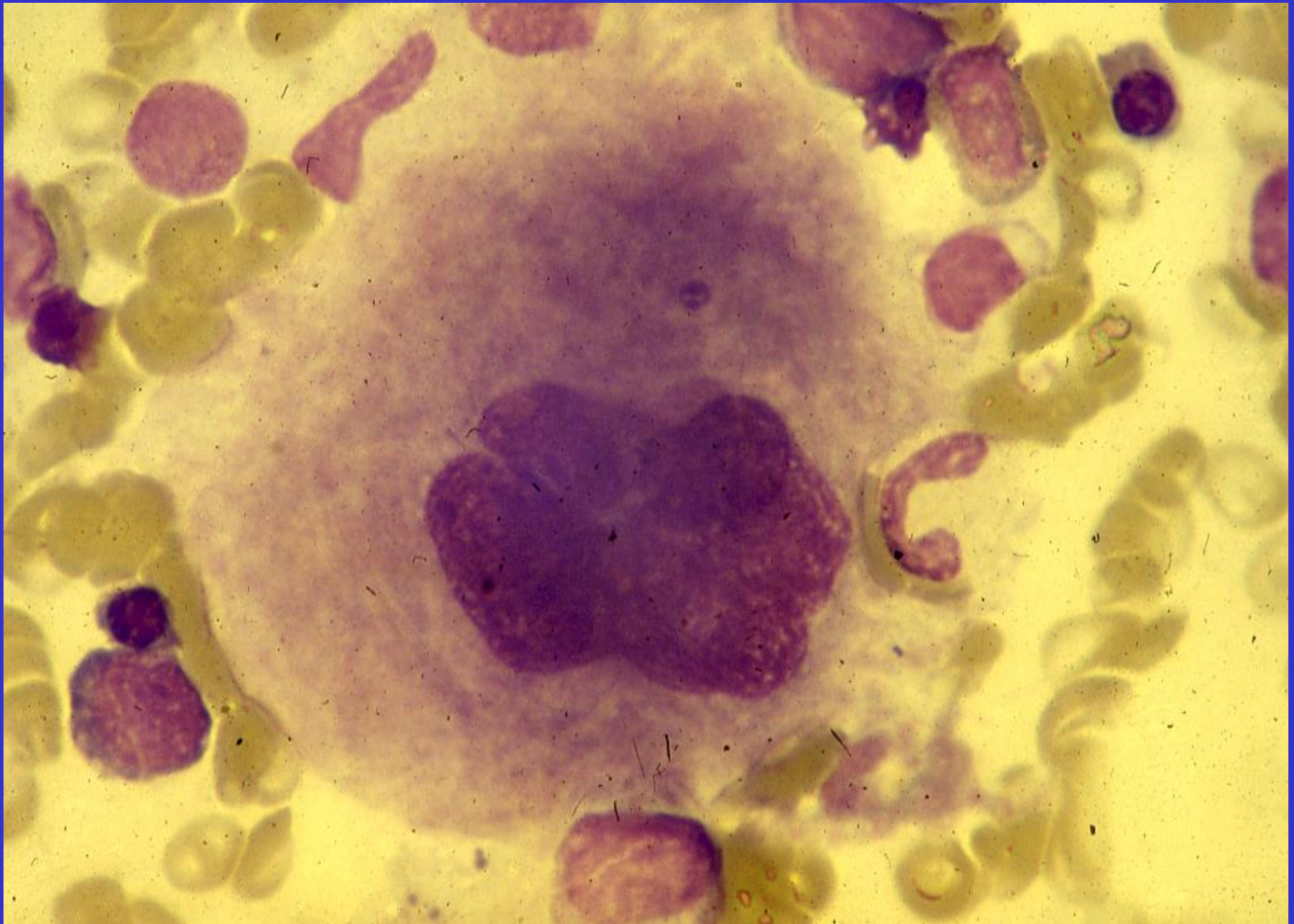
Vitamin C deficiency (Scurvy)

# THE PLATELETS

- **NORMAL PLATELET COUNT =  $150-450 \times 10^9/L$**
- **NORMAL PLATELET SIZE MPV 7.2-11.1 fl**
- **NORMAL PLATELET DIAMETER 1-3  $\mu$**
- **NORMAL PLATELET LIFE SPAN 7-10 days**
  
- **PLATELET FORMATION IS BY SEGMENTATION OF THE CYTOPLASM OF THE MEGAKARYOCYTE IN THE BONE MARROW.**



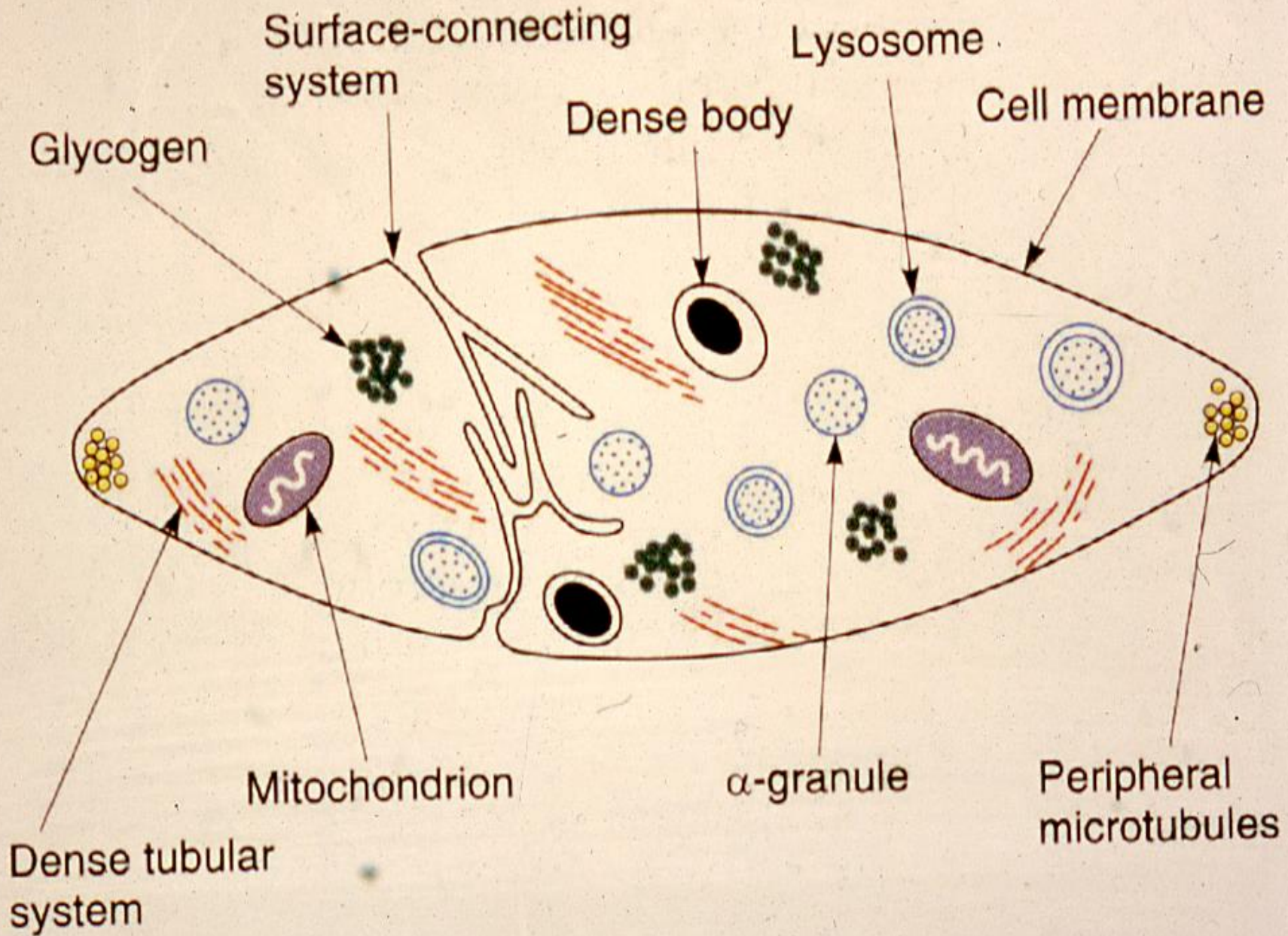




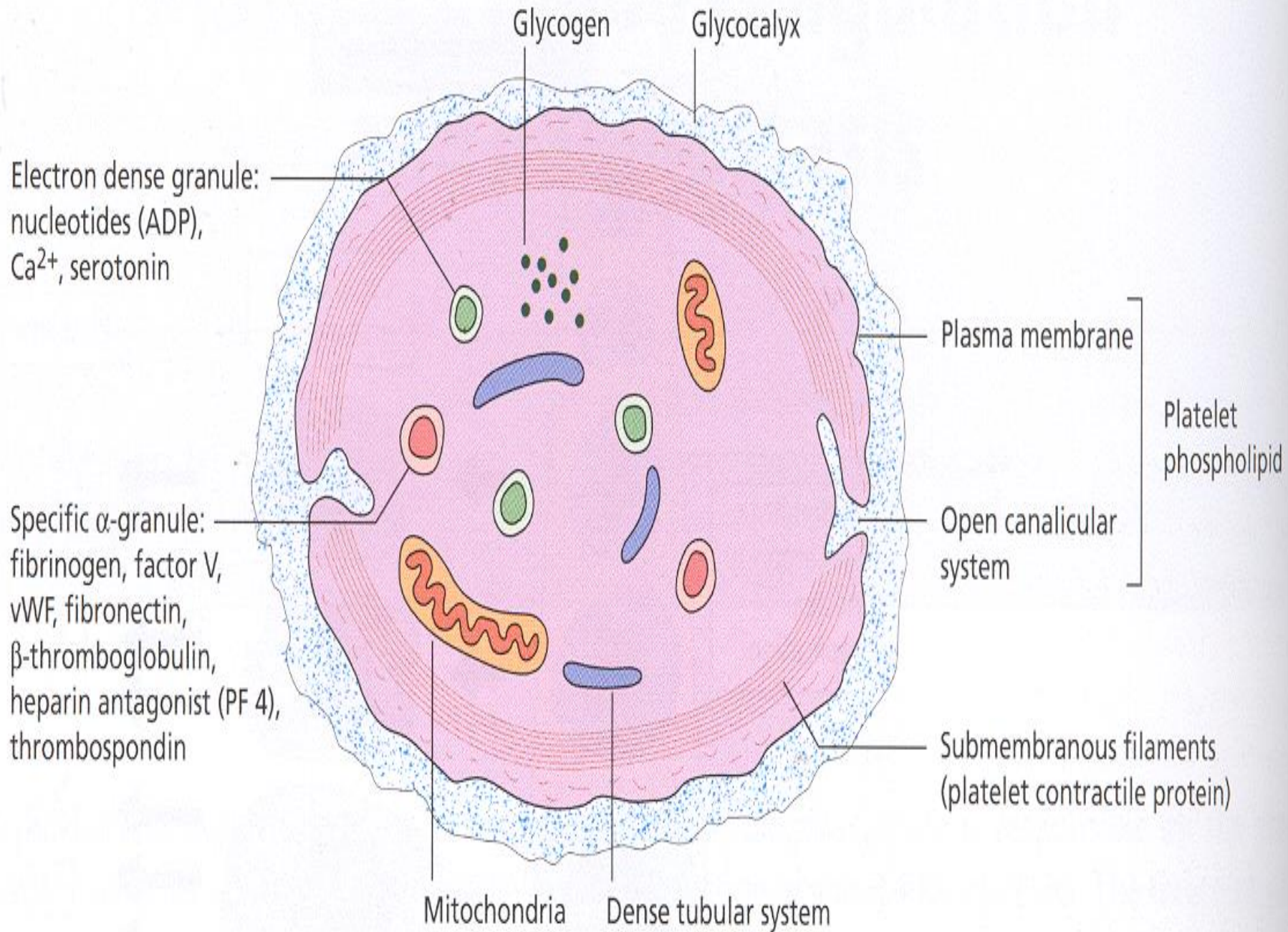




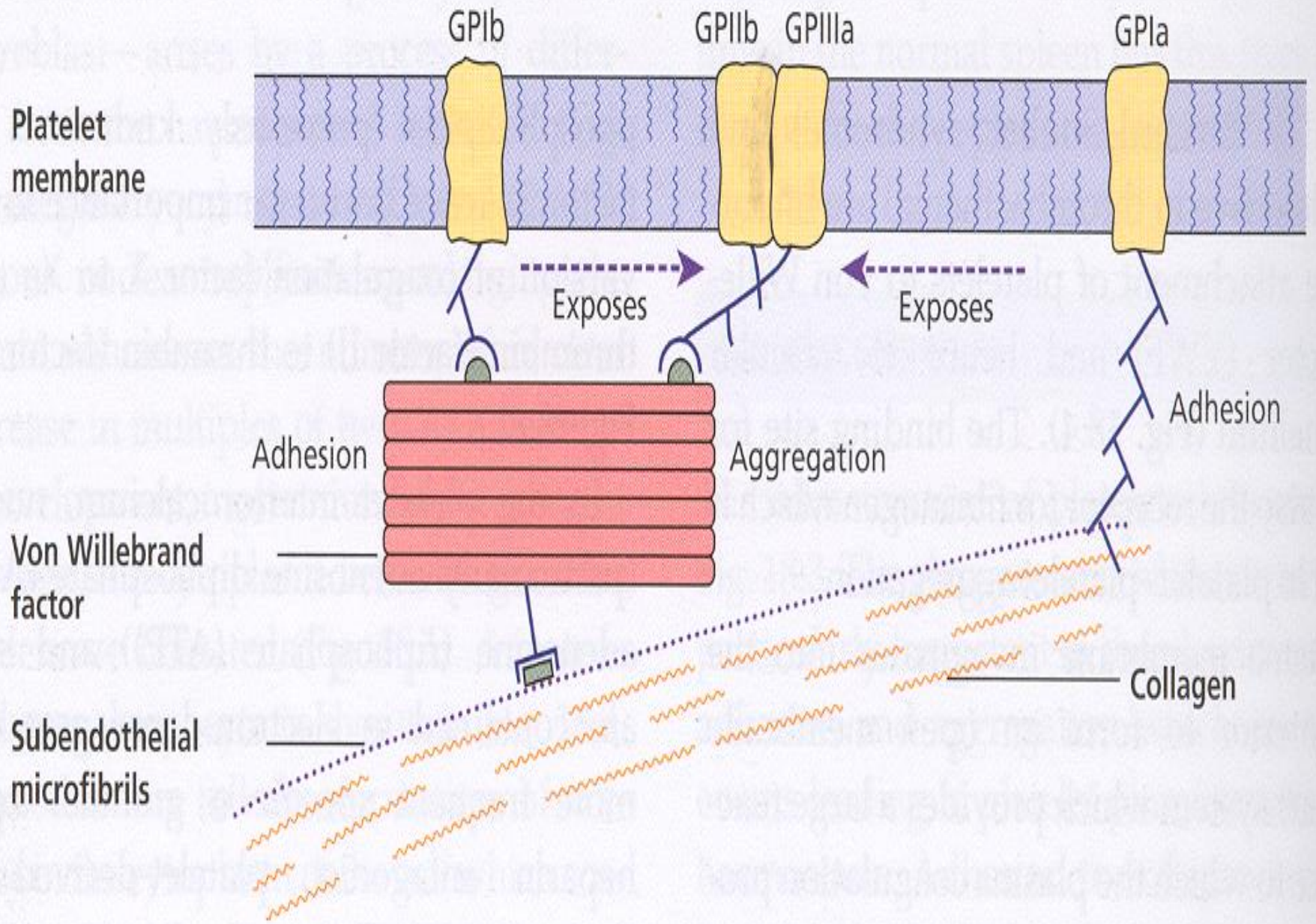






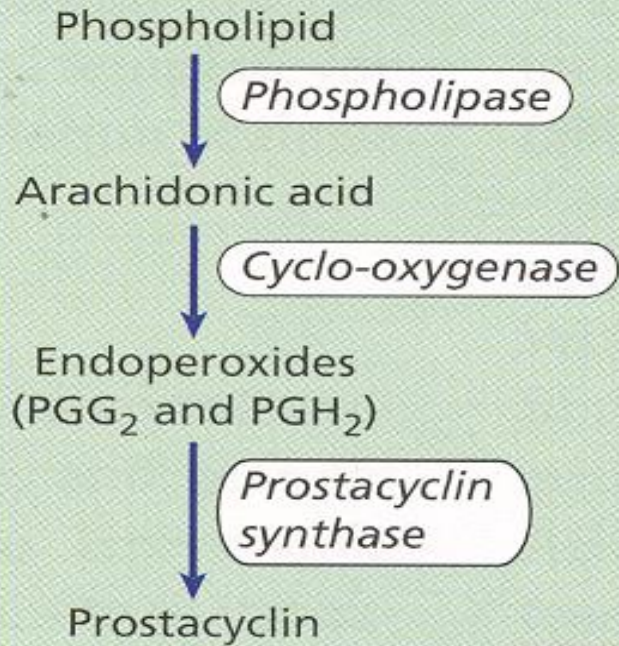




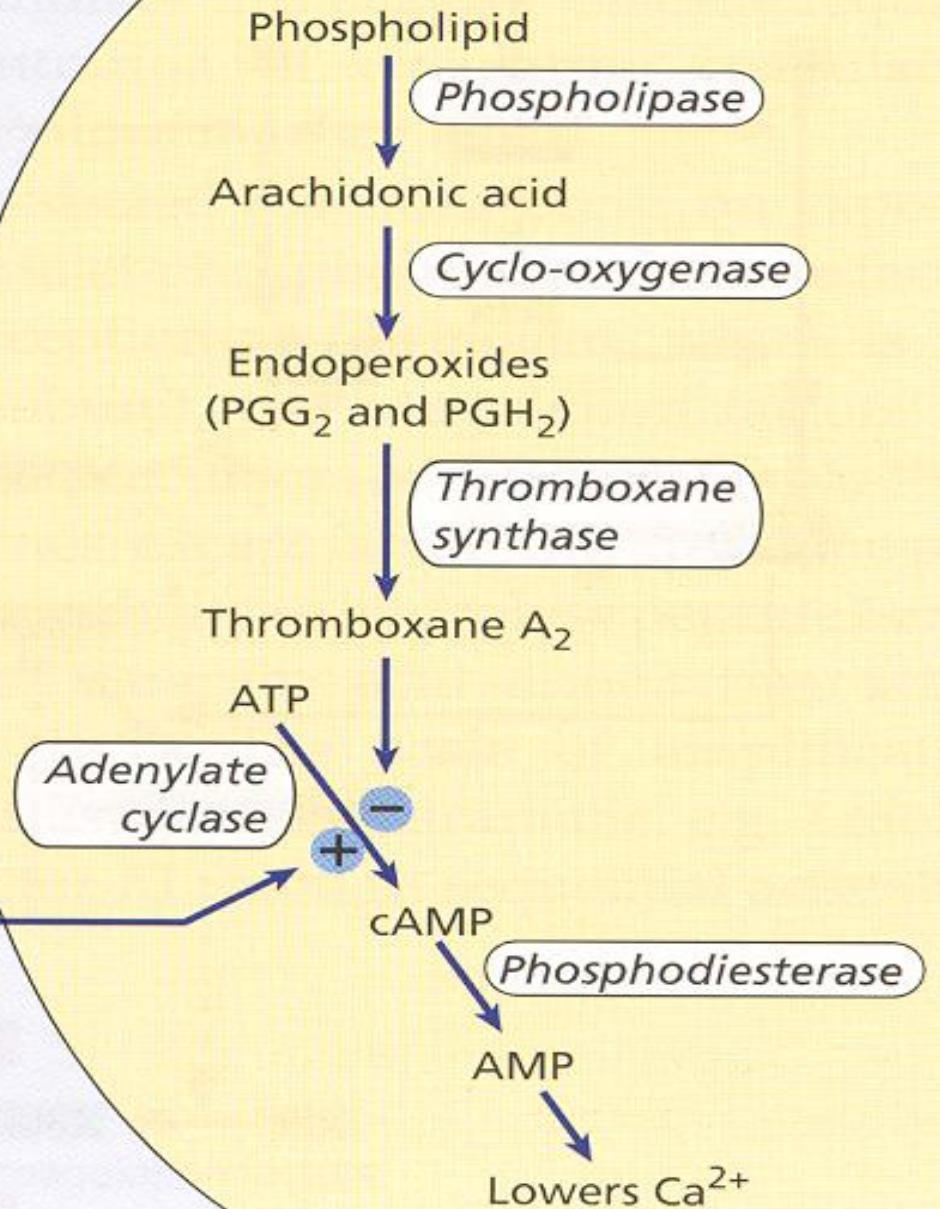


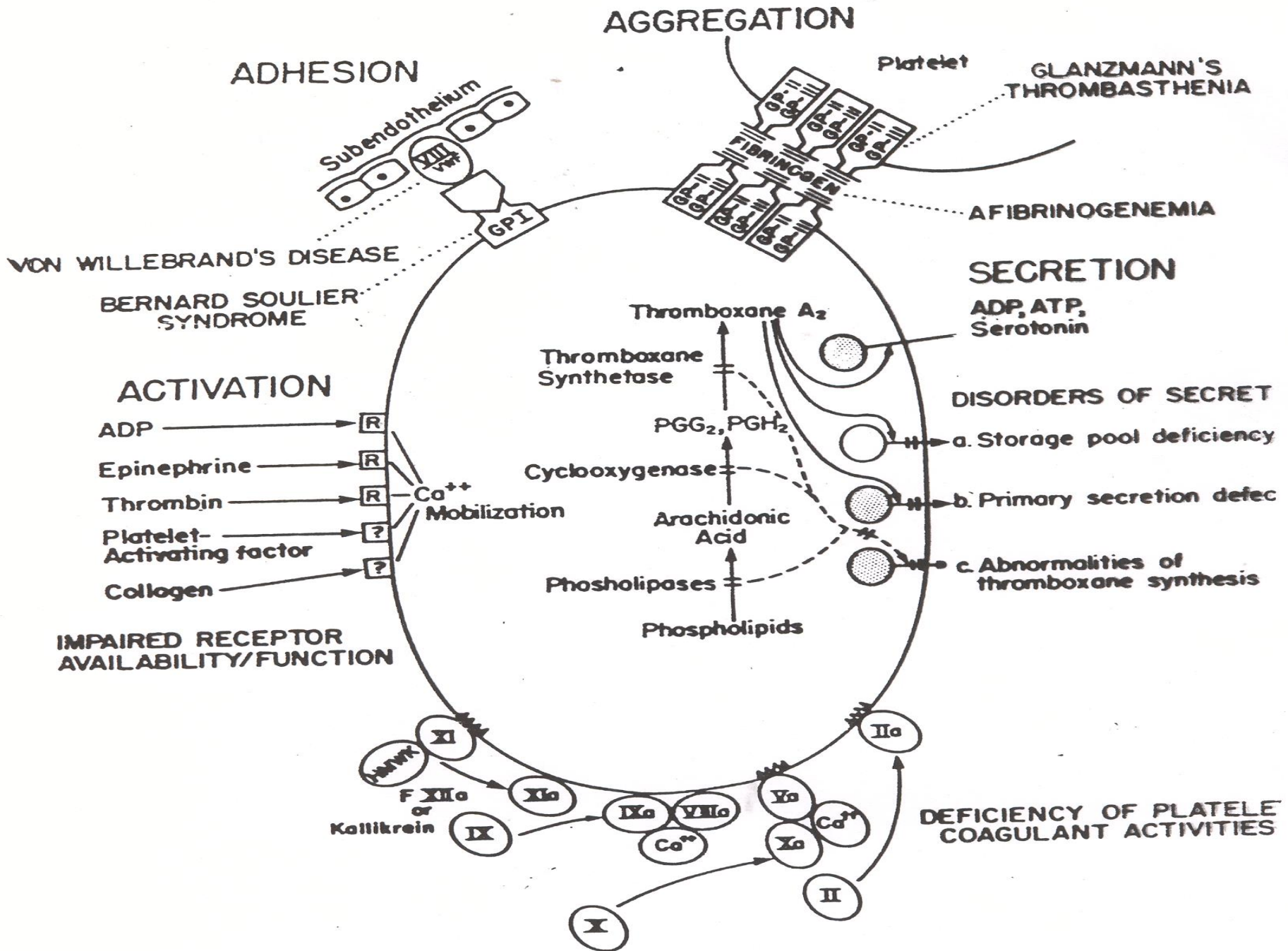


Endothelial cell

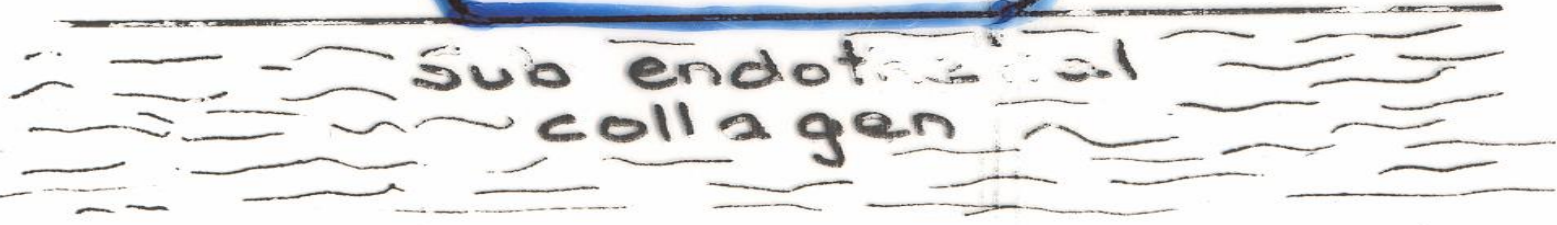
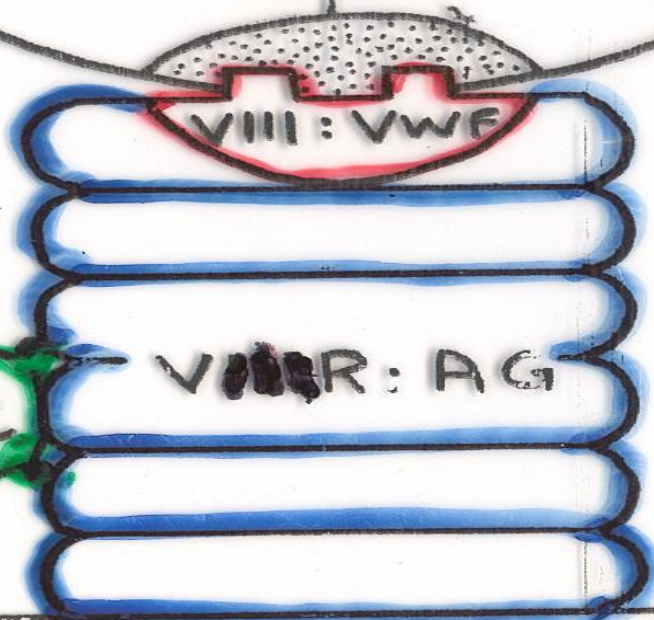


Platelet



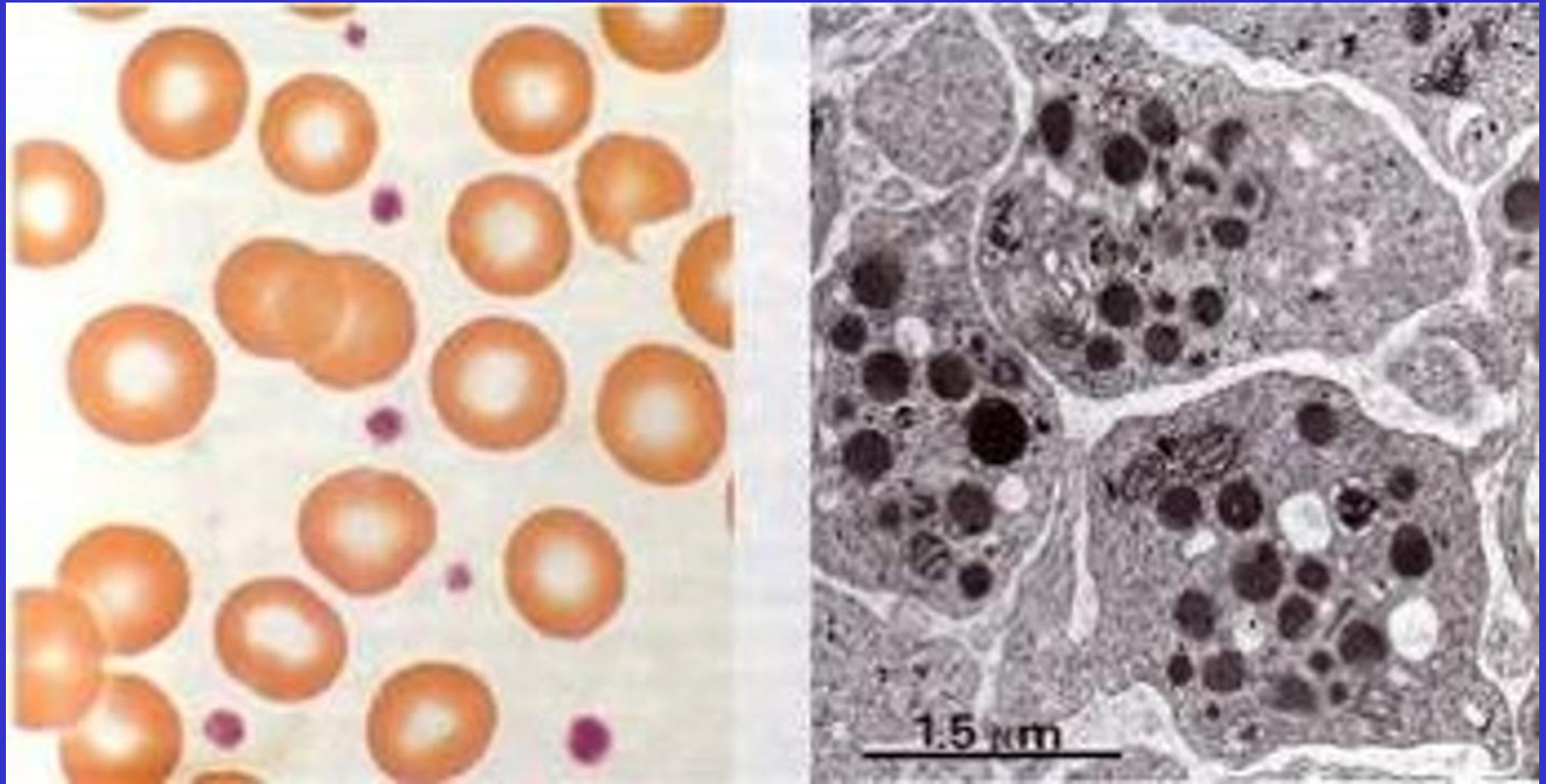












**Platelet in static forms.**

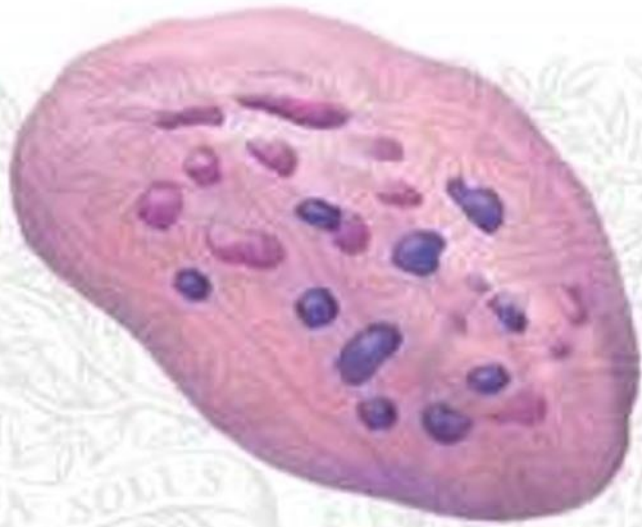
# Physiology

- The main function of platelets is the formation of a haemostatic plug at sites of damage to vascular endothelium.
- The platelets are also stimulated to produce the prostaglandin, thromboxane  $A_2$  from arachidonic acid derived from the cell membrane. The release of ADP and thromboxane  $A_2$  causes an interaction of other platelets with the adherent platelets and with each other (secondary platelet aggregation), thus leading to the formation of a platelet plug (primary haemostasis).
- At the site of injury, tissue factor (TF) is expressed and the TF-VIIa complex initiates the formation of a fibrin clot within and around the platelet plug (secondary haemostasis)
- Platelets are also responsible for the contraction of the fibrin clot once it has been formed.

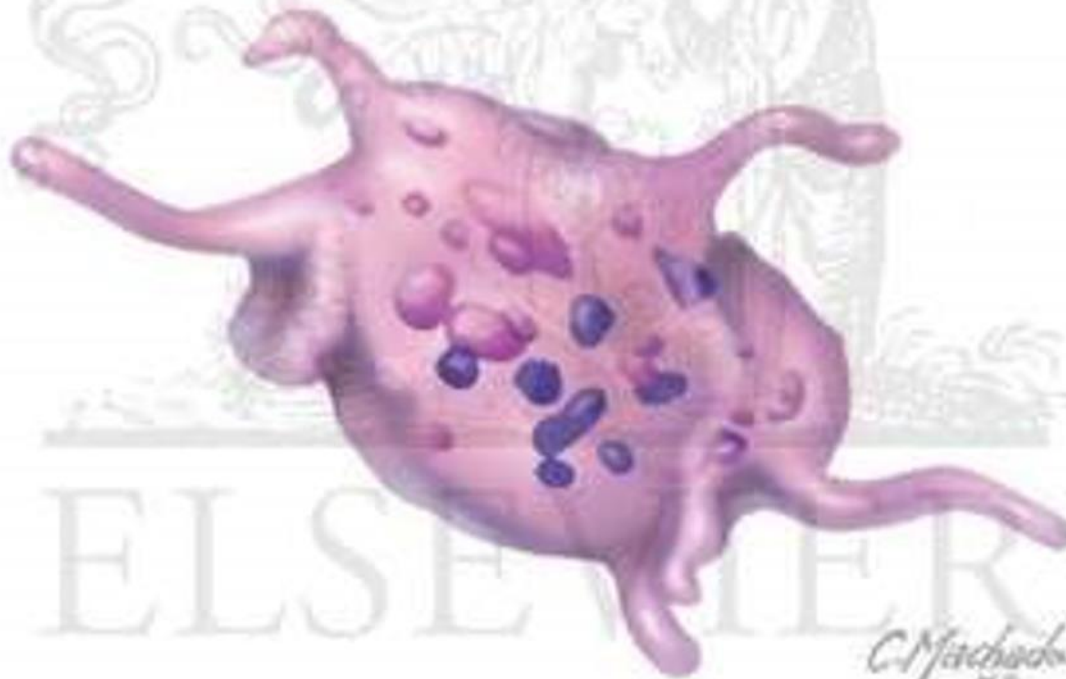
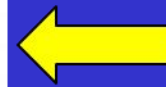


# Platelet Activation

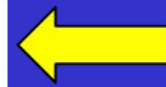
- Stickiness
- Shape Change
- Internal Contraction
- Secretion

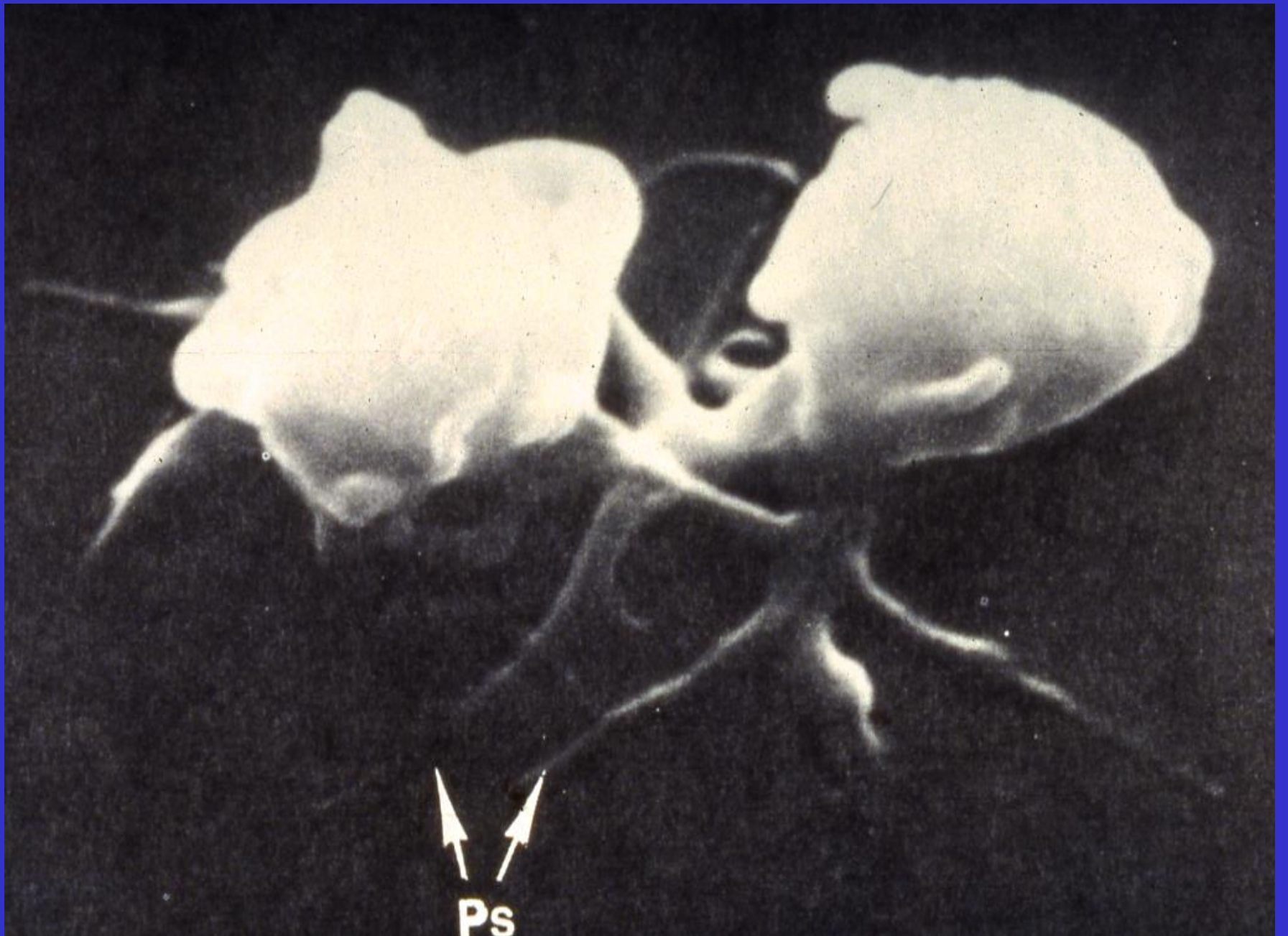


**Platelet in  
static form.**



**Platelet in  
activated  
form.**









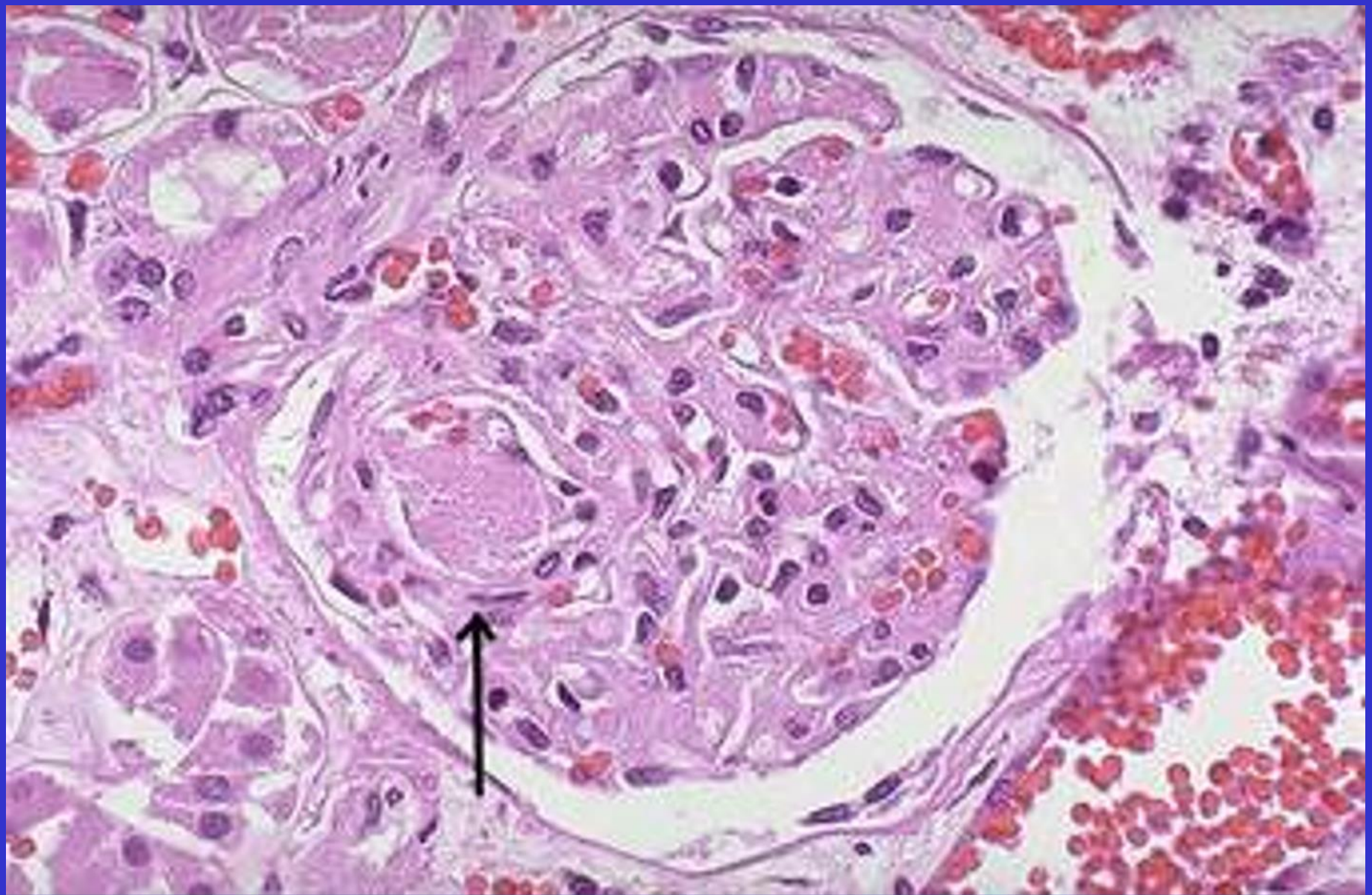
**Early platelet fibrin hemostatic plug.**





**Late platelet fibrin hemostatic plug.**





**Organized hemostatic plug.**

# Measurements of Platelet Function

# Tests of platelet function

## Bleeding time

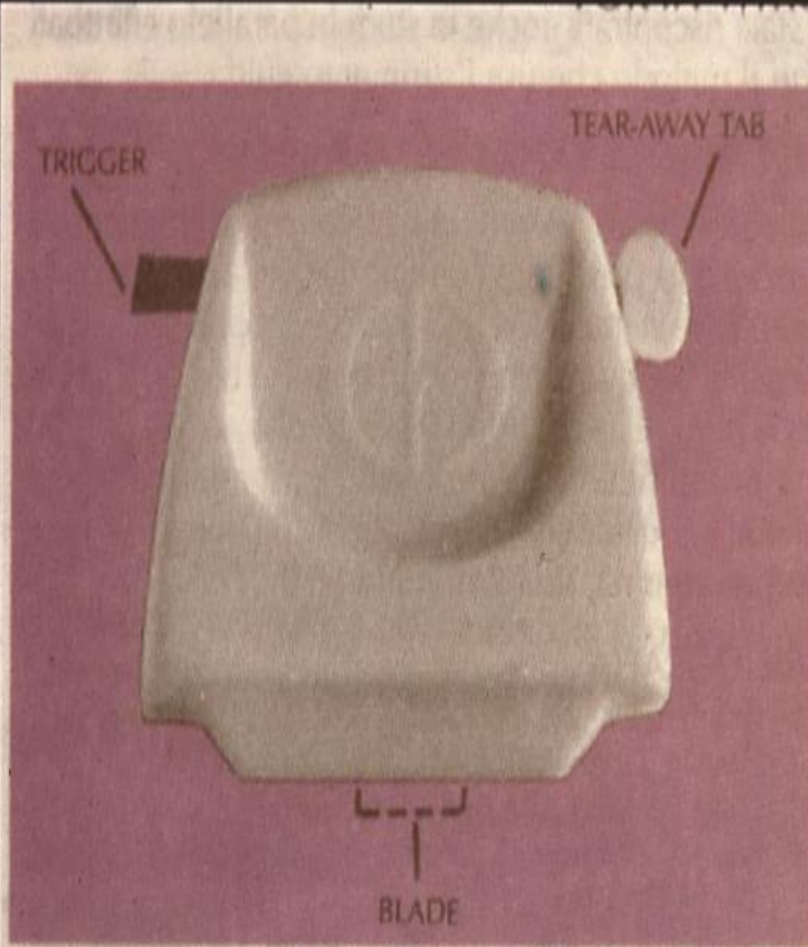
The bleeding time is estimated by making small wounds in the skin of the forearm after applying a blood pressure cuff to the upper arm and inflating it to 40mmHg; the average time that elapses until bleeding ceases is then measured.

### **PFA - 100 / PFA - 200**

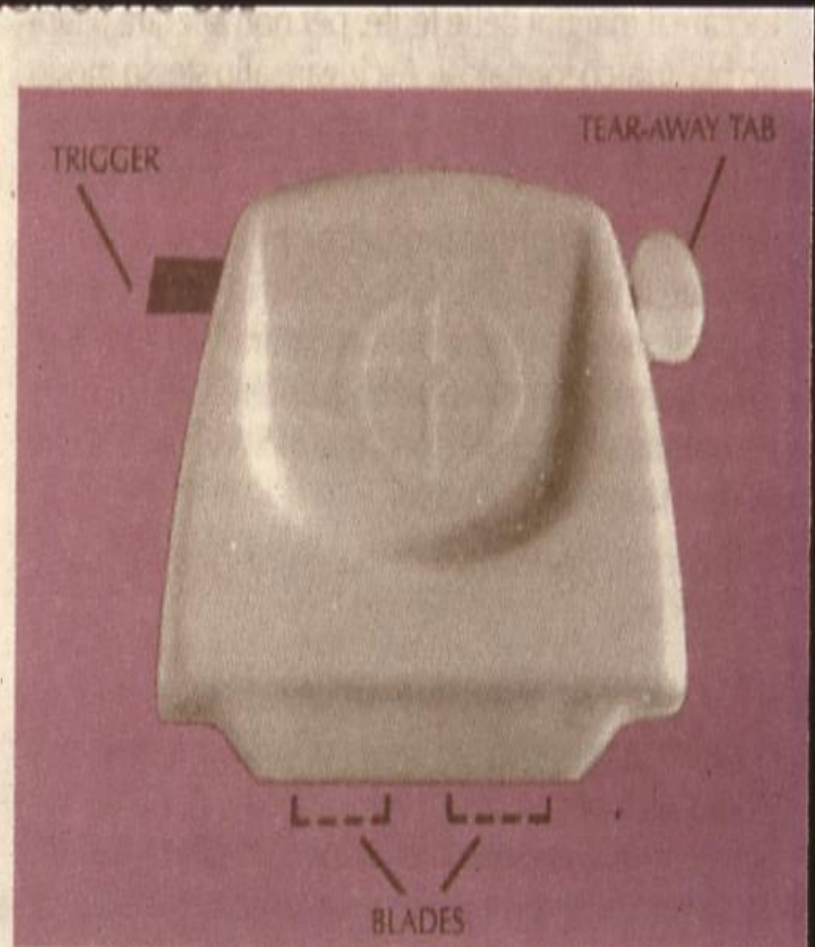
The bleeding time has largely been replaced by an *in vitro* estimation of primary haemostasis using a machine called a PFA-100.



# BLEEDING TIME

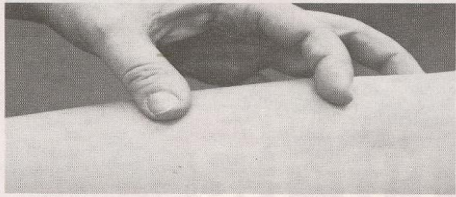


SIMPLATE

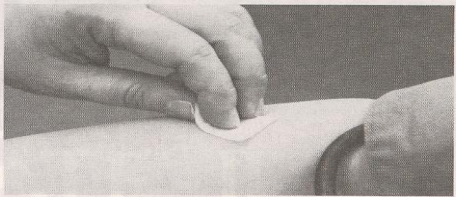


SIMPLATE-II

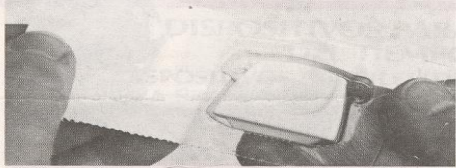




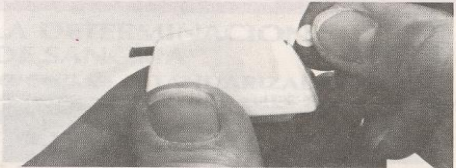
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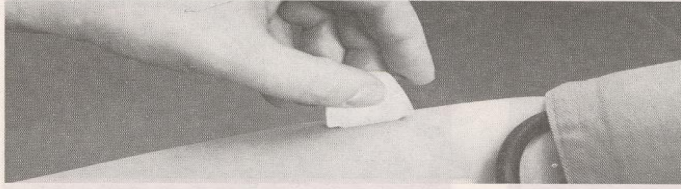
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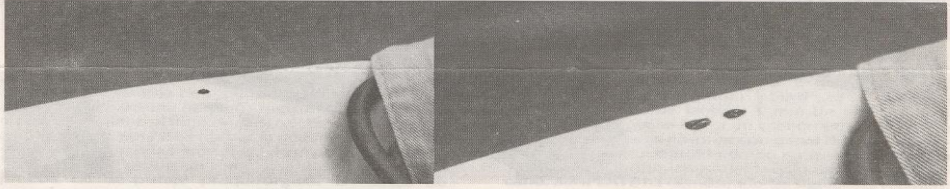
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4



5



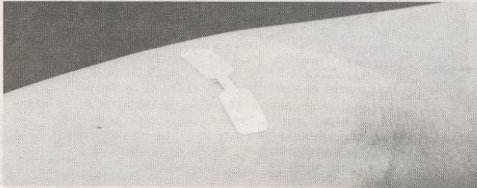
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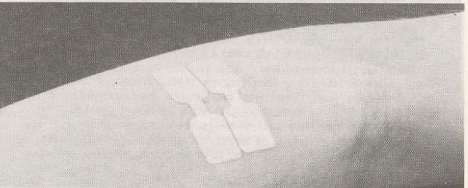
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8



9





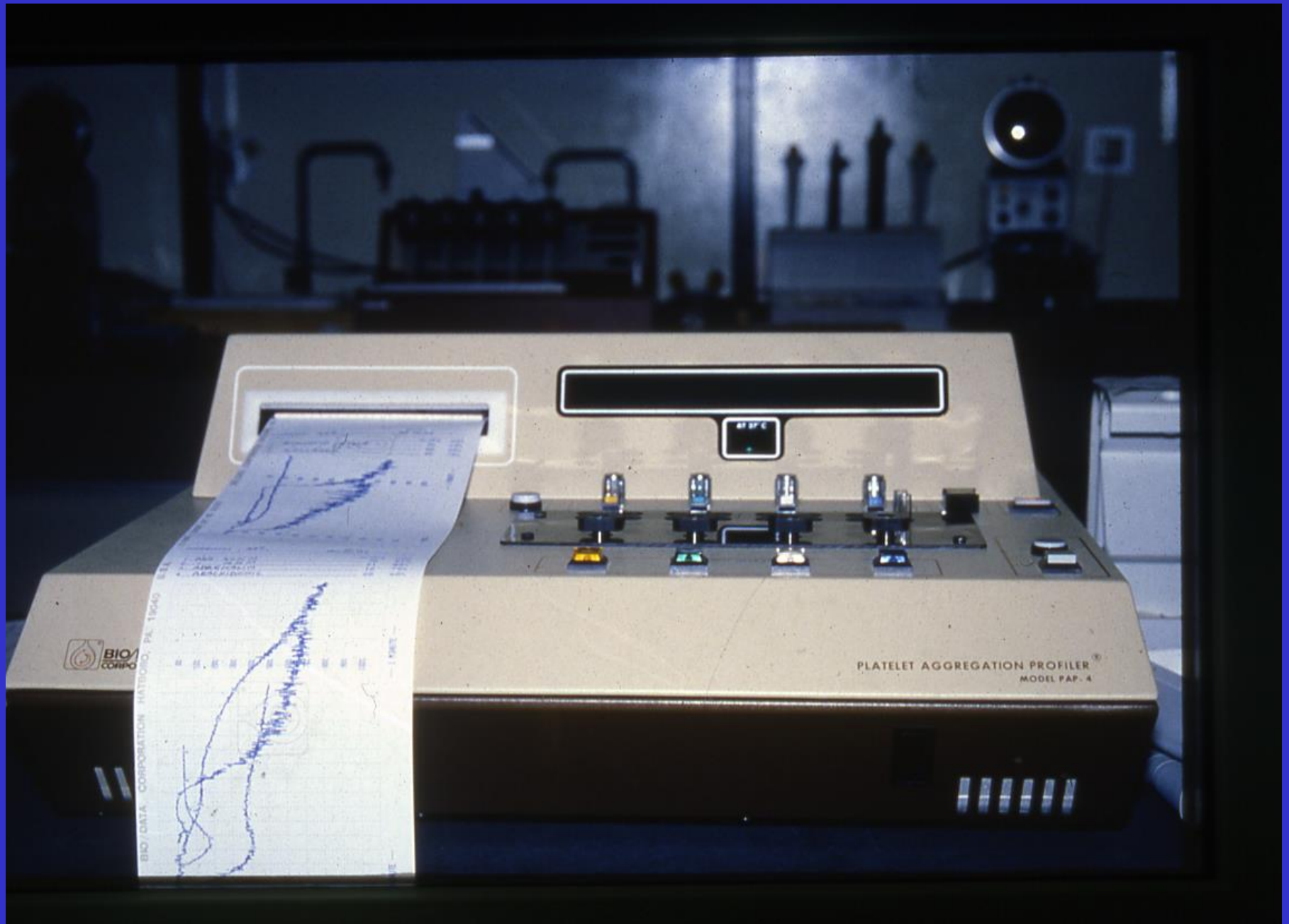
**PFA - 200**

# Platelet Aggregation



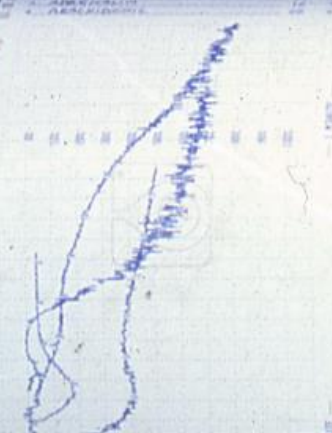
# Platelet aggregation studies

The most common is light transmission aggregometry, whereby the aggregation of platelets is studied following the addition of substances such as ADP, epinephrine, arachidonate, collagen and ristocetin to platelet-rich plasma. Aggregation causes an increase in the light transmitted through the sample and the test is performed using special equipment capable of continuously recording light transmission.



BIO/  
CORPORATION

BIO/DATA CORPORATION HATFIELD, PA. 19340

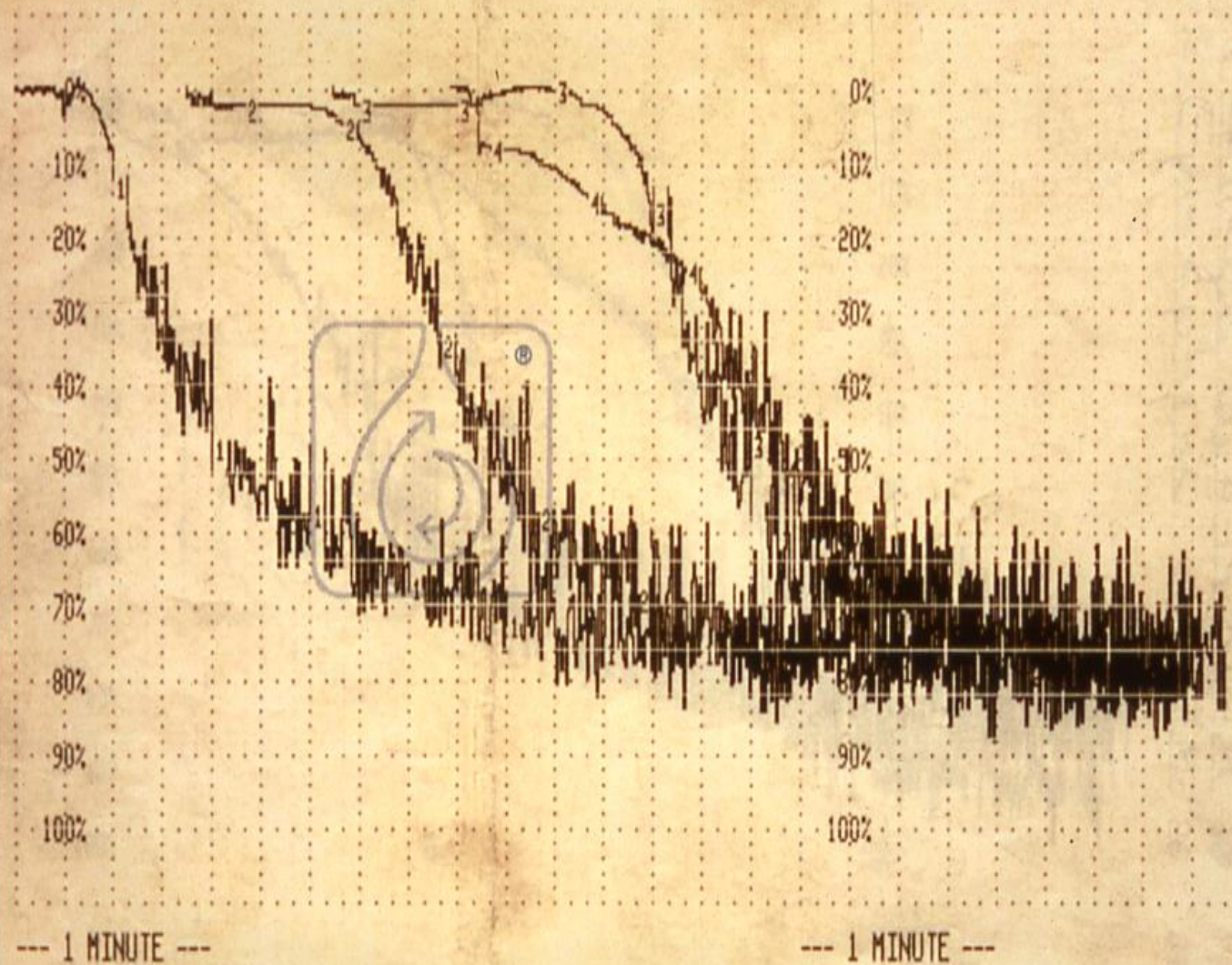


37.5°C

PLATELET AGGREGATION PROFILER<sup>®</sup>  
MODEL PAP-4

1	ADSP	2X 155 M	42	80%
2	AKA	Chudovic	34	80%
3	Collegen	0.19 mg fuel	42	80%
4	Spina-Phine	1X 10 <sup>-4</sup> M	26	77%

SLOPE AGG





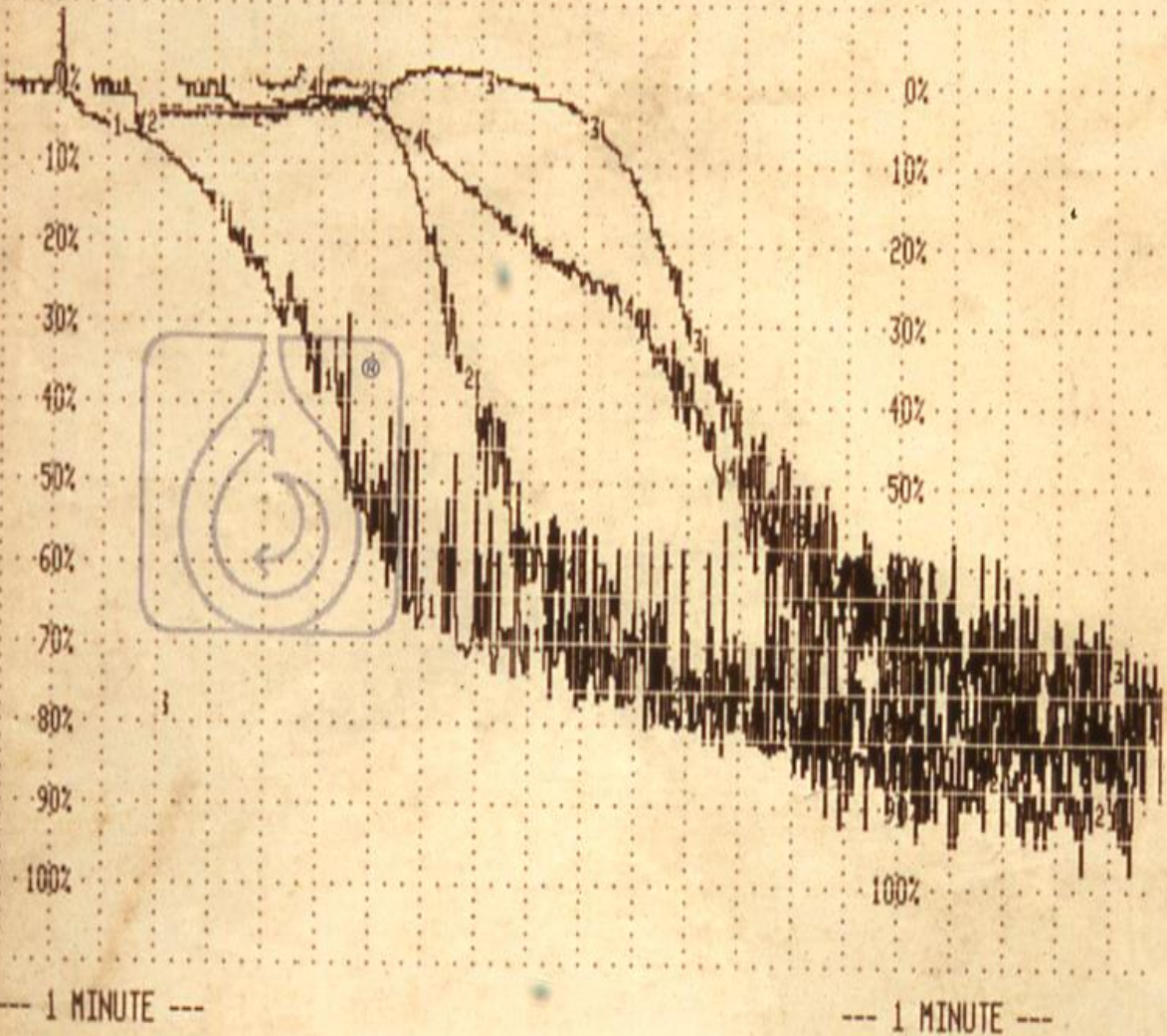
Dr. Shekaf Al Mas Kradane

COMMENTS:

DATE:

4/9/12  
8/8/192

1 Ristrelin - 1.5	SLOPE	31	AGG	80%
2 Collagen's - 0.19 mg/ml		45		91%
3 Collagen D <sub>2</sub> 0.19 mg/ml		30		76%
4 Epirin Phos - 1x10 <sup>4</sup> m		26		81%



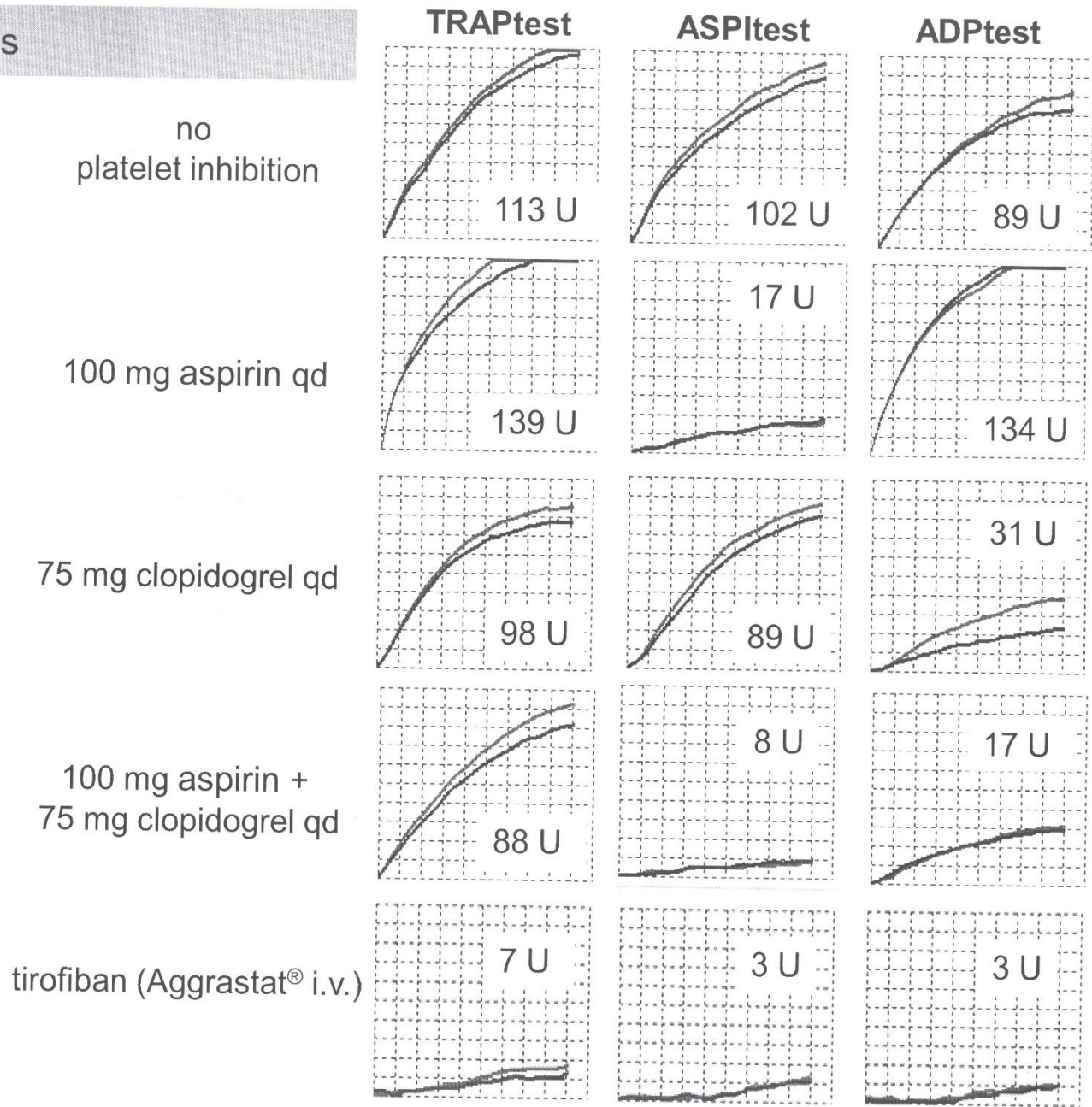


# MULTIPLATE

## Multiple Electrode Aggregometer



► examples





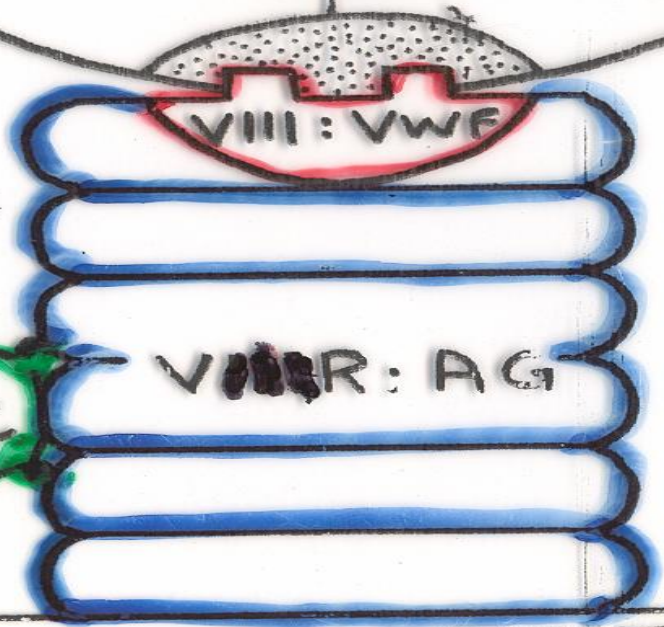
**HEREDITARY  
PLATELET DISORDERS**

# Inherited disorders of platelet function

- **Membrane abnormalities**
  - Bernard – Soulier syndrome
  - Thrombasthenia (Glanzmann's Disease)
  - Platelet factor – 3 deficiency
- **Intracellular abnormalities**
- **Storage-pool (dense body) deficiency**
  - Hermansky – Pudlak syndrome
  - Wiskott – Aldrich syndrome
  - Chediak – Higashi syndrome
  - Thrombocytopenia with absent radii
  - Idiopathic storage – pool disease
- **Storage-pool ( $\alpha$ - granule) deficiency**
  - Gray platelet syndrome
  - Combined deficiency of dense bodies and  $\alpha$  granules
- **Defects of thromboxane synthesis**
  - Cyclo-oxygenase deficiency
  - Thromboxane synthetase Deficiency
  - Defective response to thromboxane
- **Miscellaneous**
  - Epstein's syndrome
  - May-Hegglin anomaly

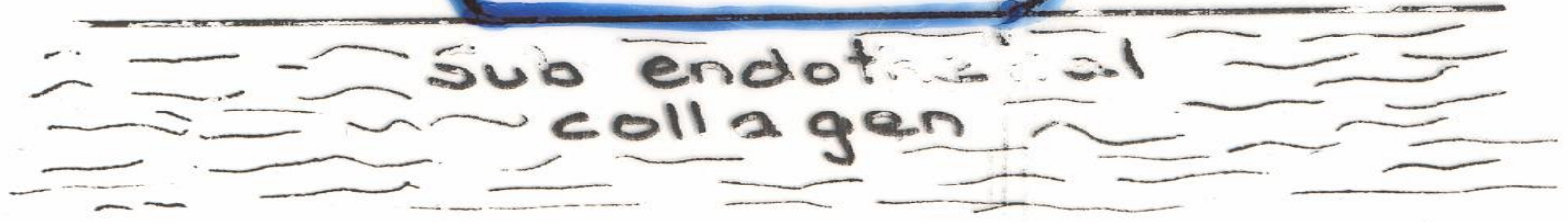






VIII: C

VIII: R: AG



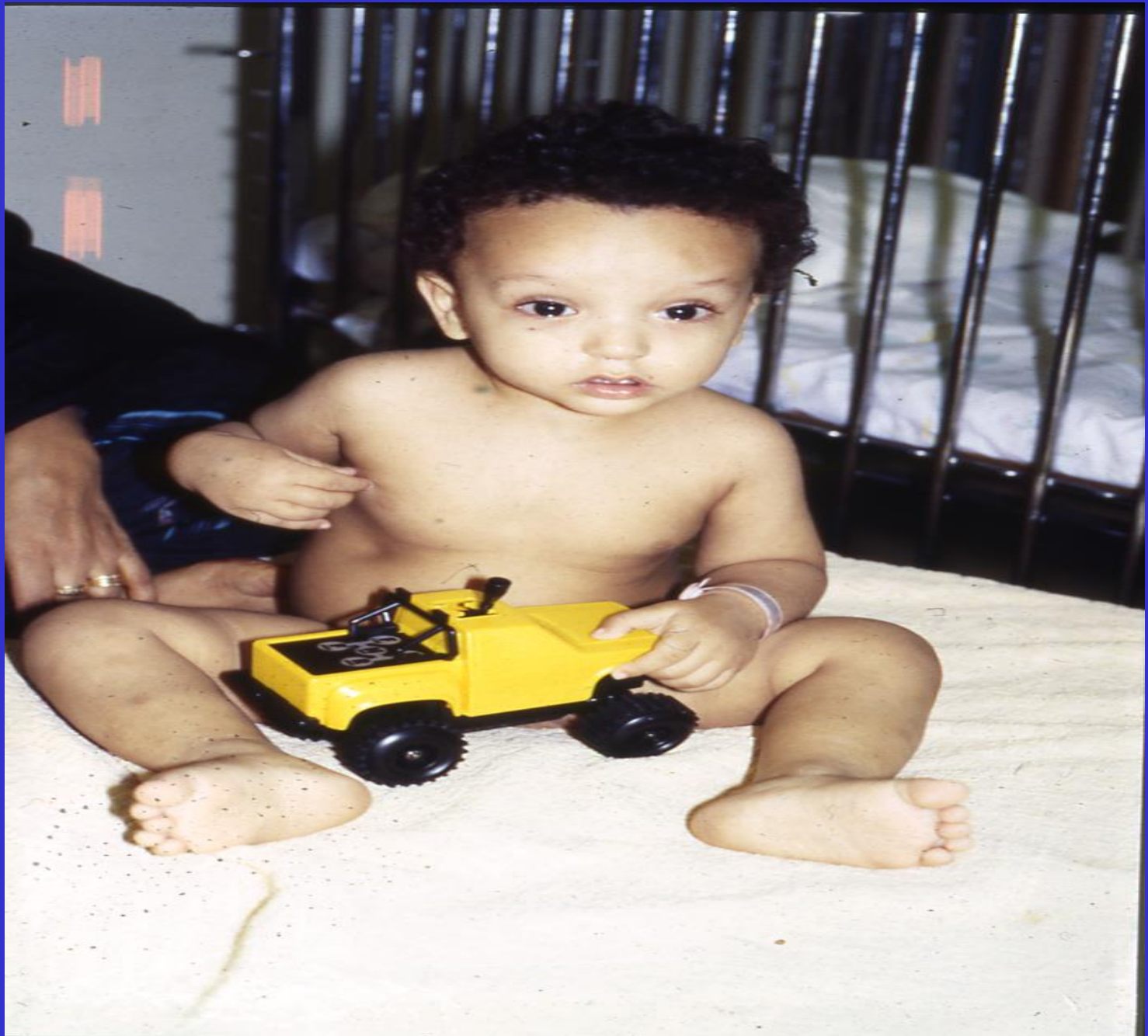
# Inherited Glanzmann's disease

This is a rare but severe platelet disorder caused by a lack of glycoprotein IIb/IIIa receptors. Inheritance is autosomal recessive and platelets are normal in morphology and number.











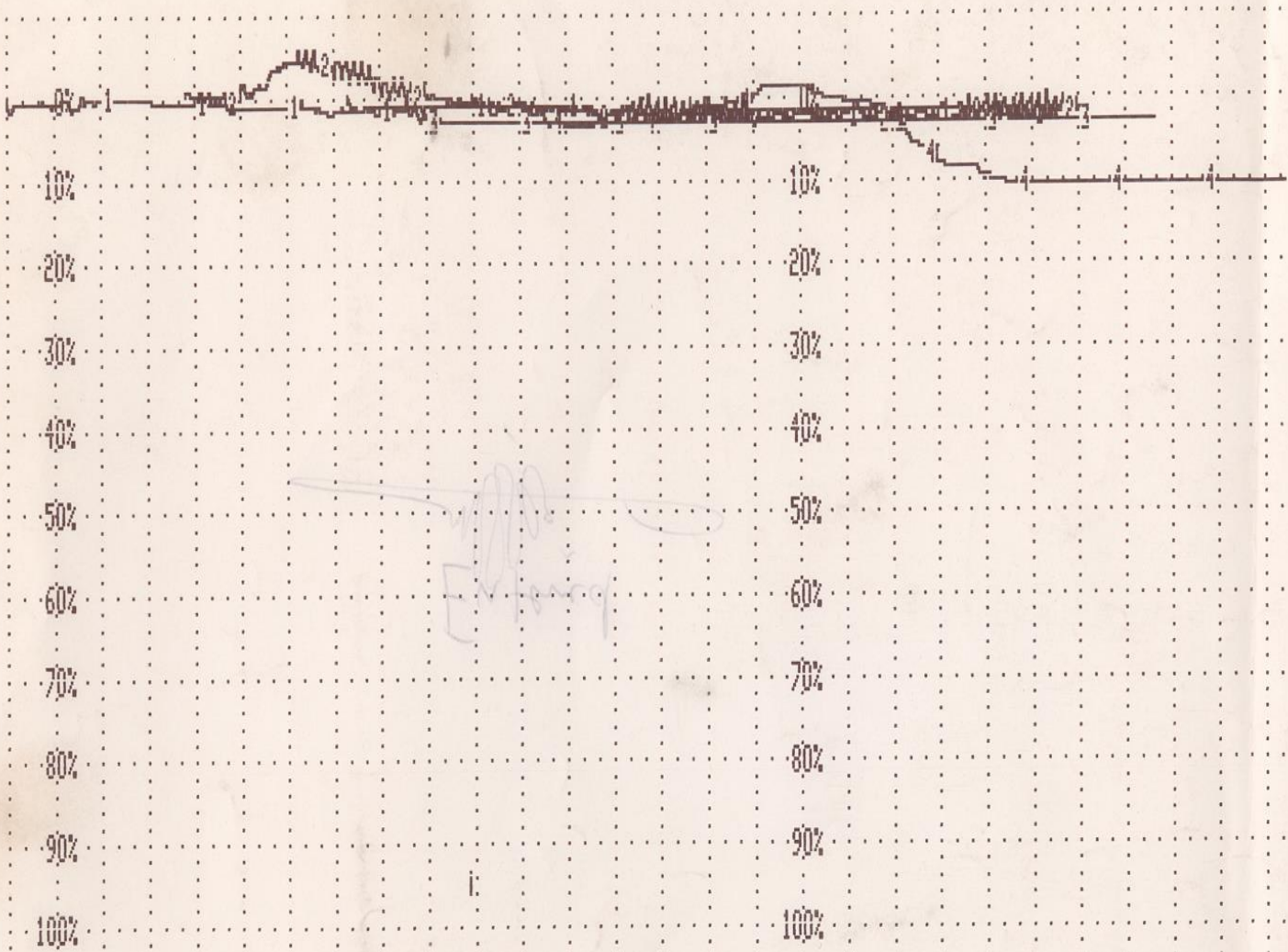




COMMENTS: 81-35-33

DATE:

	SLOPE	AGG
1 ADD BIO/DATA	03	02%
2 ARACH/DONIC	04	03%
3 ADRENALINE	04	03%
4 COLLAGEN	09	10%



--- 1 MINUTE ---

--- 1 MINUTE ---

At Rahman

Lab #

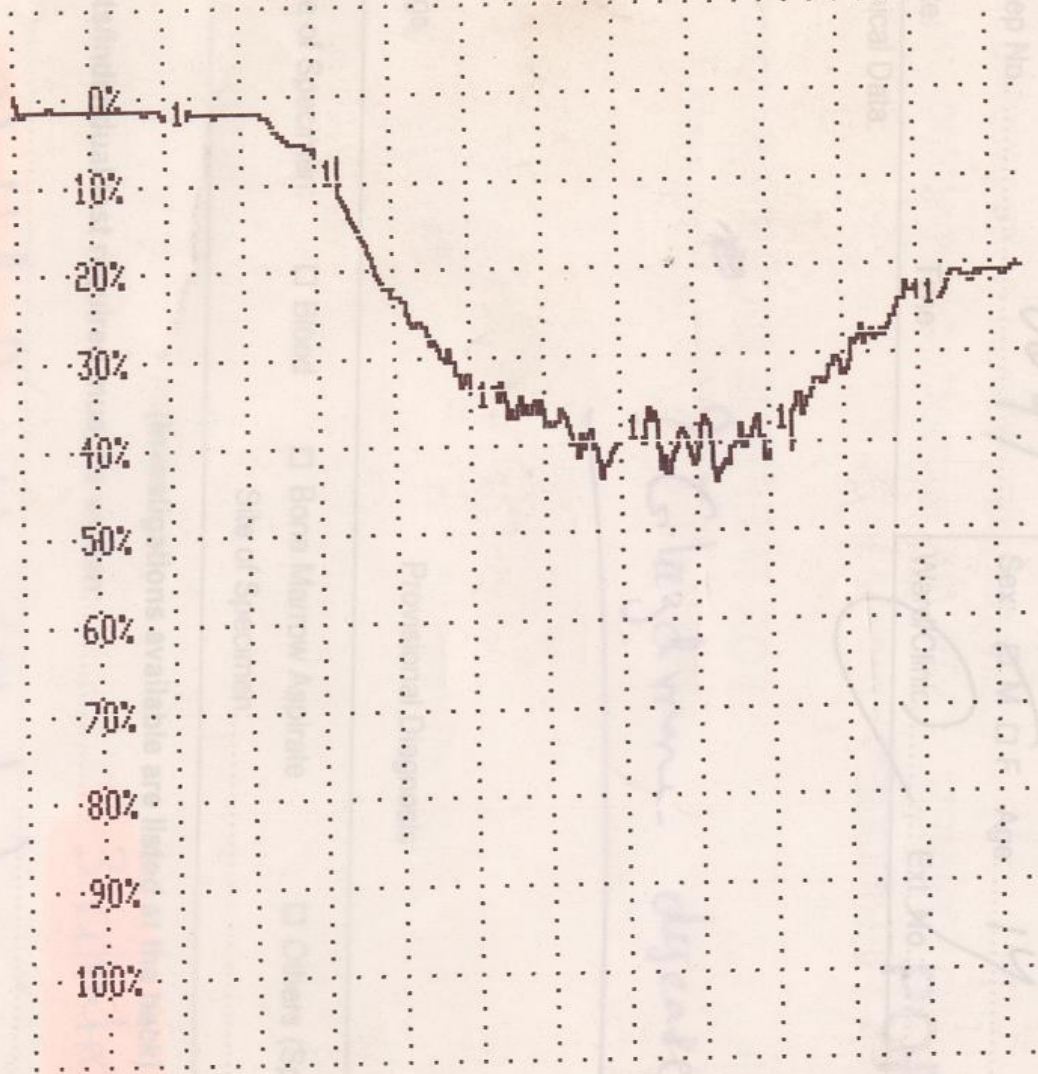


36

COMMENTS: 81-35-33

SLOPE AGG

1 Value RISTO. 1.5 mg/L 2/28 20%



--- 1 MINUTE ---

# Bernard-Soulier disease

This is a platelet disorder caused by a lack of glycoprotein Ib receptors. Inheritance is autosomal recessive. Platelets are larger than normal and usually the platelet count is reduced.



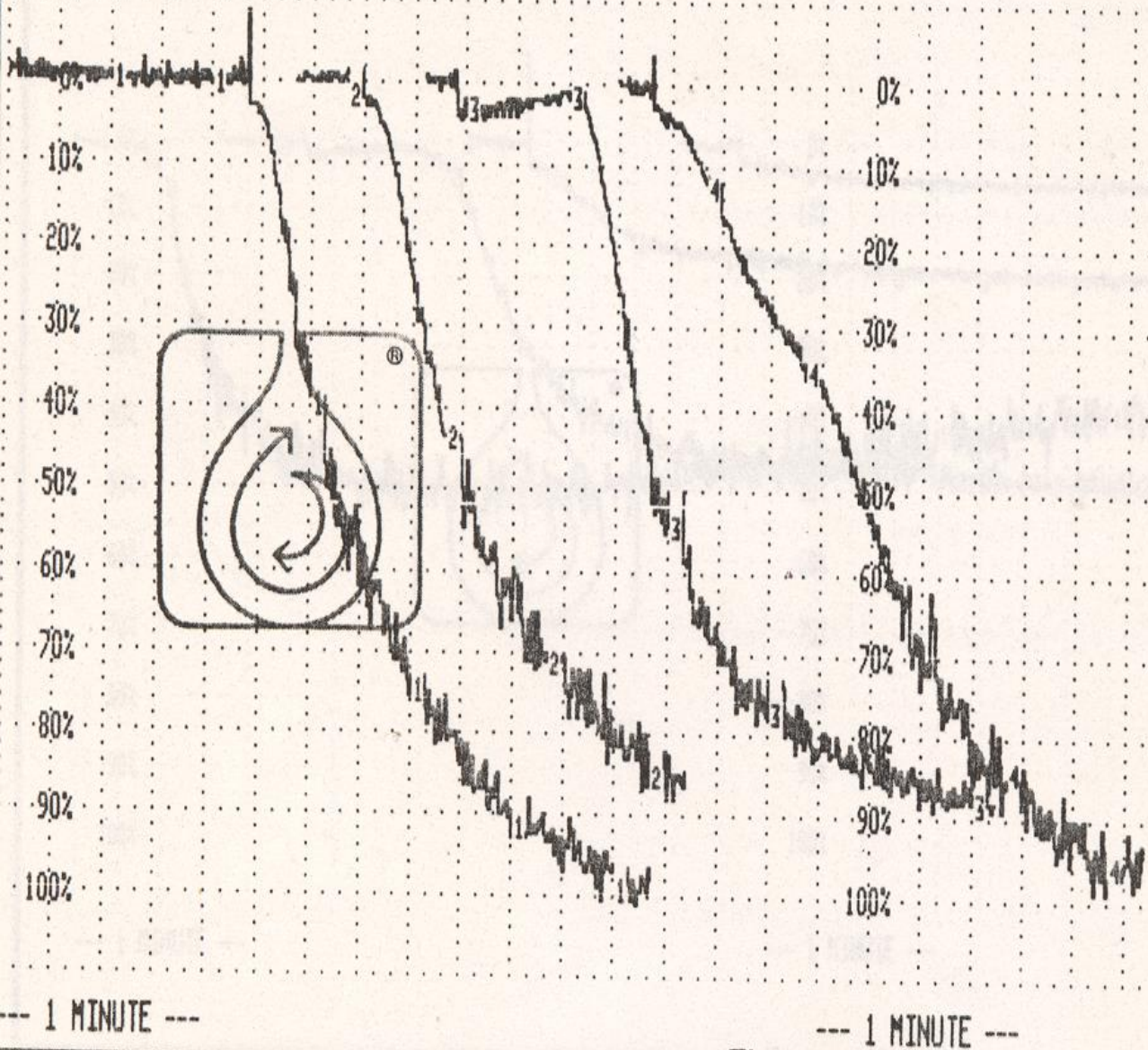
BIO/DATA CORPORATION, HATBORO, PA. 19040 U.S.A.

PRINT FROM MEMORY

DATE: 5/24

COMMENTS: NORMAL PLATELETS

	SLOPE	AGG
1 ADP $2 \times 10^{-5} M$	58	99%
2 ARACHIDONIC ACID	52	86%
3 COLLAGEN $1.9 \text{ mg/ml}$	62	89%
4 EPINEPHRINE $10^{-3} M$	30	95%



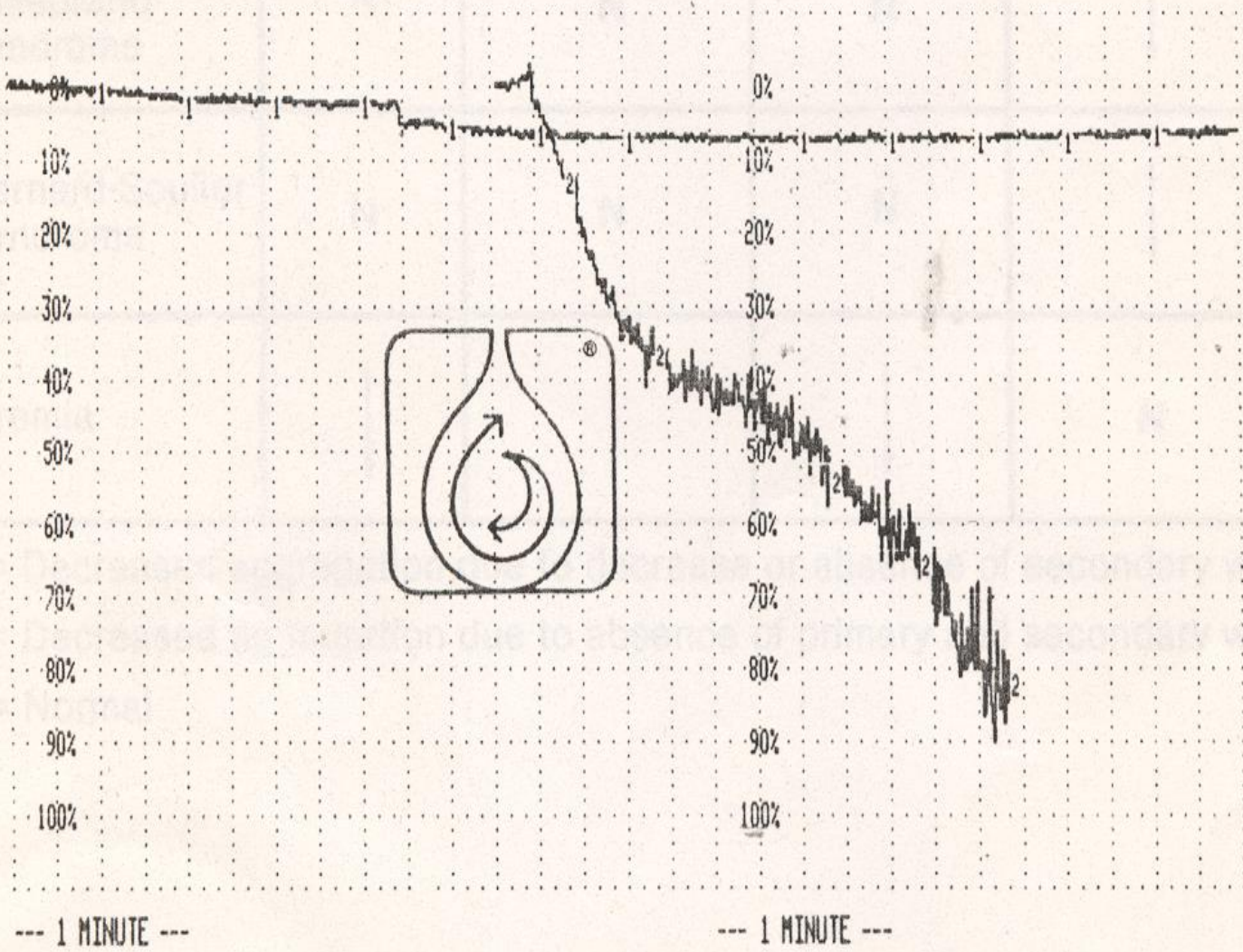


BIO/DATA CORPORATION, HATBORO, PA. 19040 U.S.A.

PRINT FROM MEMORY

COMMENTS: *Ristocetin, 1.25 mg/lat* DATE: *5/24*

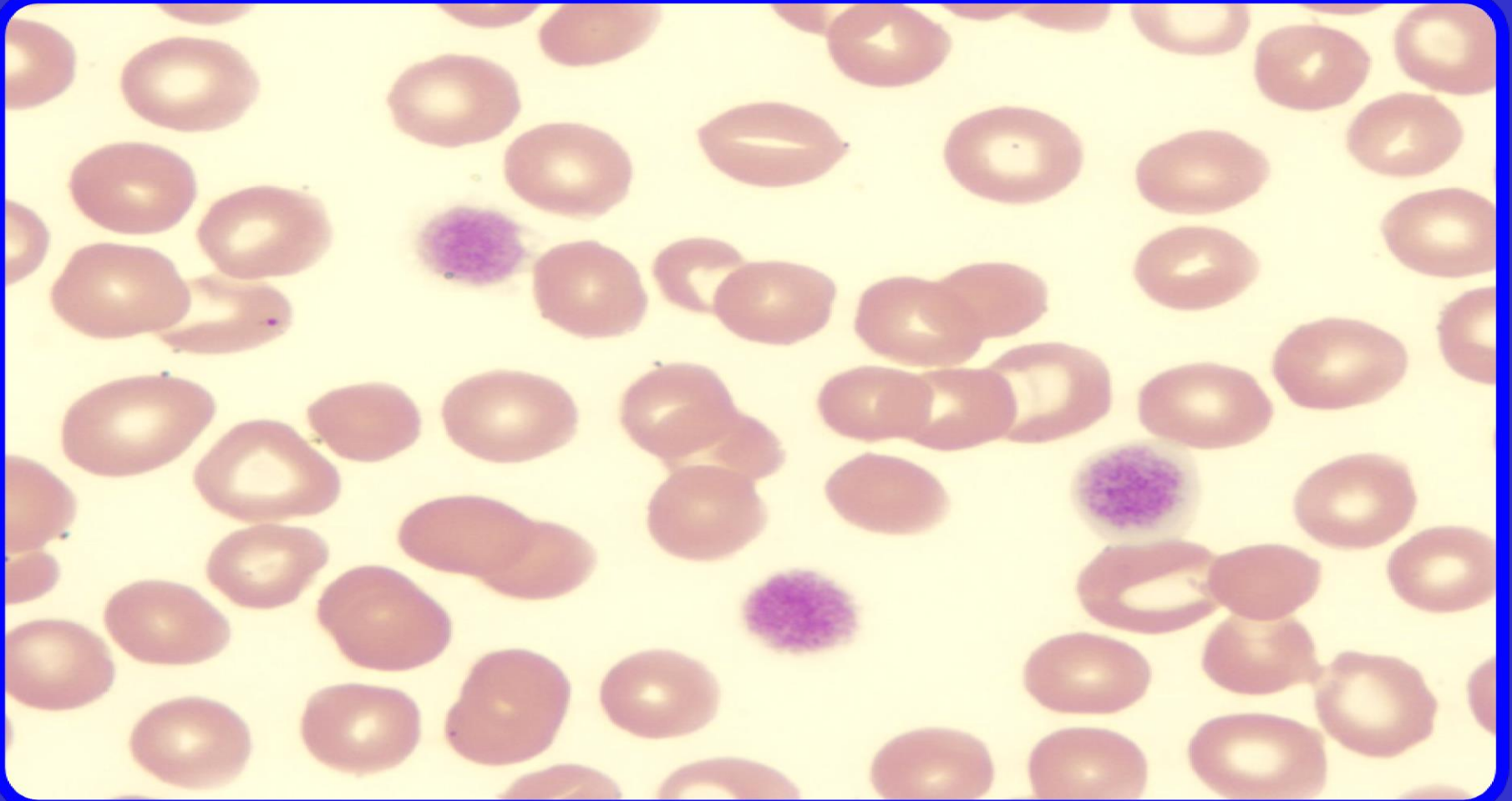
1 *von Willebrand Patient* SLOPE 04 AGG 07%  
 2 *Normal Control* 31 85%



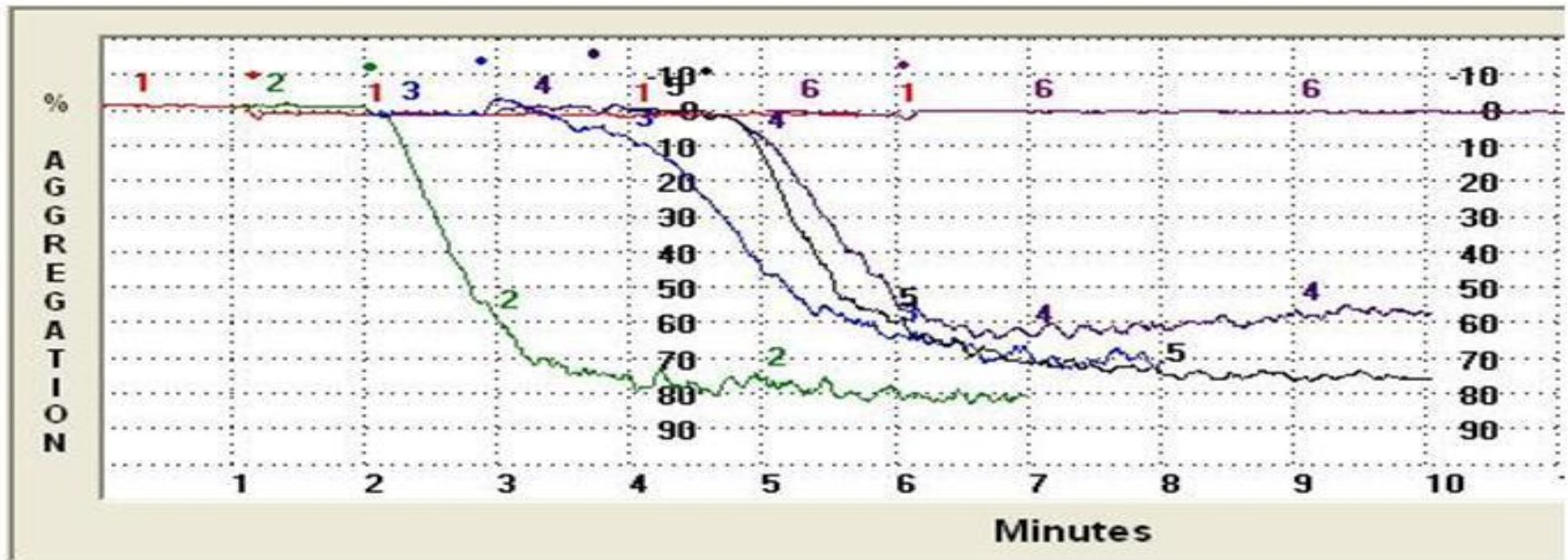
<b>Test</b>	<b>Patient</b>	<b>Reference Range</b>
<b>PT</b>	<b>12.8s</b>	<b>11.5 -13.2s</b>
<b>APTT</b>	<b>27s</b>	<b>26-32s</b>
<b>Fibrinogen (Clauss)</b>	<b>2.9g/L</b>	<b>2-4 g/L</b>
<b>Platelets</b>	<b>45 x 10<sup>9</sup>/L</b>	<b>150-450 x 10<sup>9</sup>/L</b>

Haemostatic profile from a patient with Bernard-Soulier syndrome.





Blood film picture from a patient with Bernard-Soulier syndrome showing very large platelets (giant platelets).



- 1 Ristocetin 1.5 mg/ml
- 2 AA
- 3 Collagen

- 4 ADP
- 5 Epinephrine
- 6 Ristocetin 0.5 mg/ml

The results of platelet aggregation tests in a patient with Bernard-Soulier syndrome.

# Storage pool diseases

These are inherited conditions resulting in defective platelet granules ( $\alpha$  granules or dense body granules or both).



ADP

Collagen

Arachidonate

Ristocetin

Thrombasthenia



Bernard-Soulier Syndrome



Storage Pool Deficiency



Defects of Thromboxane Synthesis



Normal



Aggregation patterns in platelet disorders.

# Causes of Acquired Platelet Dysfunction

- Uraemia
- Myeloproliferative Disorders
- Acute Leukaemias and Myelodysplastic Syndrome
- Paraproteinaemias
- Chronic Hypoglycemia
- Liver Disease
- Valvular and Congenital Heart Disease
- Severe Burns
- Scurvy
- Drugs (aspirin etc.)

# Acquired Abnormalities of platelet function

- An acquired defect of platelet function is found after ingestion of aspirin and other antiplatelet drugs.
- Other causes of an acquired abnormality of platelet function include chronic myeloproliferative disorders, myelodysplastic syndromes, paraproteinaemias (e.g. myeloma or Waldenström's macroglobulinaemia) and uraemia.



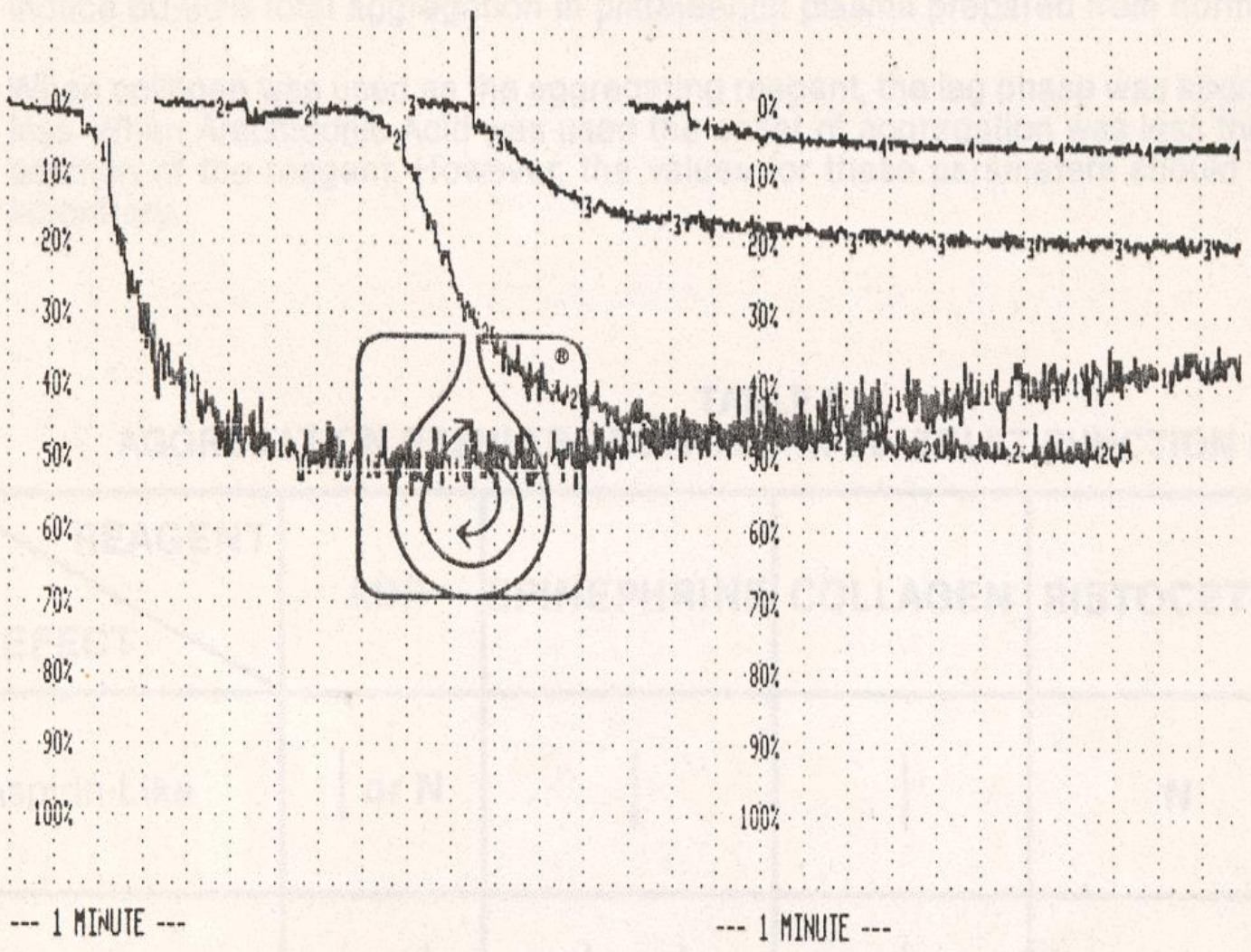
BIO/DATA CORPORATION, HATBORO, PA. 19040 U.S.A.

PRINT FROM MEMORY

DATE: 5/84

COMMENTS: Abnormal Platelets  
Aspirin ingestion

	SLOPE	AGG
1 ADP 8X10 <sup>-5</sup> M	42	33%
2 Collagen 0.19 mg/ml	27	48%
3 Epinephrine 10 <sup>-5</sup> M	09	20%
4 Quinidine Quil	07	06%



--- 1 MINUTE ---

--- 1 MINUTE ---

# THROMBOCYTOPENIA

# Causes of thrombocytopenia

## Bone Marrow Failure

- Bone Marrow failure of platelet production
  - **Selective megakaryocyte depression in the bone marrow**  
rare congenital defects (amegakaryocytic aplasia)
  - **drugs, chemicals, viral infections**
  - **Part of general bone marrow failure**
  - **cytotoxic drugs**
  - **radiotherapy**
  - **aplastic anaemia**
  - **leukaemia**
  - **myelodysplastic syndromes**
  - **myelofibrosis**
  - **marrow infiltration e.g. carcinoma, lymphoma**
  - **multiple myeloma**
  - **megaloblastic anaemia**
  - **HIV infection**



## Causes of thrombocytopenia (continued)

### Increased consumption of platelets in the peripheral blood

#### ➤ Immune

- **autoimmune (idiopathic)**
- **associated with systemic lupus erythematosus, chronic lymphocytic leukaemia or lymphoma**
- **feto-maternal alloimmune thrombocytopenia**
- **post-transfusional purpura**

#### ➤ infections: HIV, other viruses, malaria

#### ➤ drug-induced (e.g. heparin induced thrombocytopenia)

#### ➤ Disseminated intravascular coagulation

#### ➤ Thrombotic thrombocytopenic purpura

#### ➤ Abnormal distribution of platelets

- **Splenomegaly**

#### ➤ Dilutional loss

- **Massive transfusion of stored blood to bleeding**

# Increased splenic pooling

- ❖ A normal spleen contains within its microcirculation about 30% of all the blood platelets.
- ❖ The splenic platelet pool increases with increasing splenic size, so that in patients with moderate to massive splenomegaly it may account for 50-90% of all blood platelets, thus causing thrombocytopenia.

A newborn baby with allo-immune thrombocytopenia showing widespread purpura all over the body.

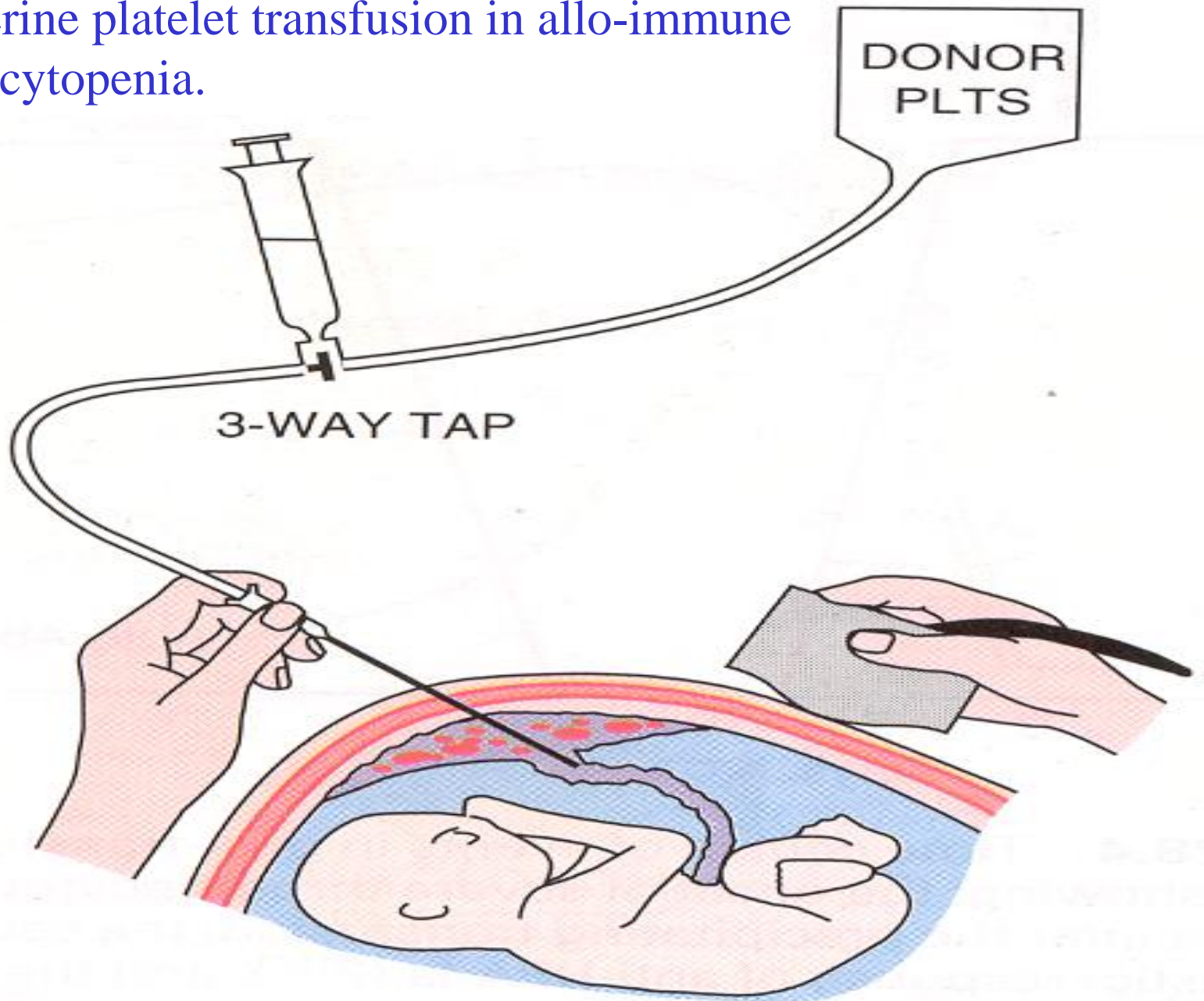








Intra-uterine platelet transfusion in allo-immune thrombocytopenia.



# Immune thrombocytopenic purpura (ITP)

ITP is characterized by petechiae, bruising, spontaneous bleeding from mucous membranes and a reduction in the platelet count. The disease presents in both an acute and a chronic form.



# Clinical features

## Acute ITP

This is seen at all ages but is most common before the age of 10 years. Two-thirds of patients give a history of a common childhood viral infection (e.g. upper respiratory tract infection, chicken pox, measles) 2-3 weeks preceding the purpura. Platelet counts are often less than  $20 \times 10^9/L$ . In most patients the disease runs a self-limiting course of 2-4 weeks, but in approximately 20% it becomes chronic; that is, it lasts more than 6 months. The mortality is low, the main danger being intracranial bleeding.



**Multiple pin-point haemorrhages (petechiae) on the legs of a patient with idiopathic thrombocytopenic purpura (ITP).**



**Large ecchymoses on both the upper arms of a woman with ITP.**



# Clinical features of immune thrombocytopenia

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**Degree of  
Thrombocytopenia**

**Symptoms**

**Physical findings**

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**Mild (>50 000/mm<sup>3</sup>)**

**None**

**None**

**Moderate  
(30-50 000/mm<sup>3</sup>)**

**Bruising with minor  
trauma**

**Scattered ecchymoses  
at trauma site**

**Severe (10-30 000/mm<sup>3</sup>)**

**Spontaneous bruising,  
menorrhagia**

**Petechiae and purpura,  
more prominent on  
extremities**

**Marked (<10 000mm<sup>3</sup>)**

**spontaneous brusing,  
mucosal bleeding, risk  
for CNS bleeding**

**Generalized purpura,  
epistaxis, GU bleeding  
CNS symptoms**

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*cont'd...*

## **Chronic ITP**

This occurs mainly in the age period 15-50 years; higher incidence in women than in men. Platelet counts are usually between 20 and 80  $\times 10^9/L$ . Spontaneous cures are rare and the disease is characterized by relapses and remissions.

# Diagnosis

- ❖ Children with the appropriate clinical features, acute thrombocytopenia and an otherwise normal blood count (i.e. no evidence of acute leukaemia).
- ❖ In ITP, bone marrow megakaryocytes are normal or increased in number (up to four-or eightfold) and increased in size.













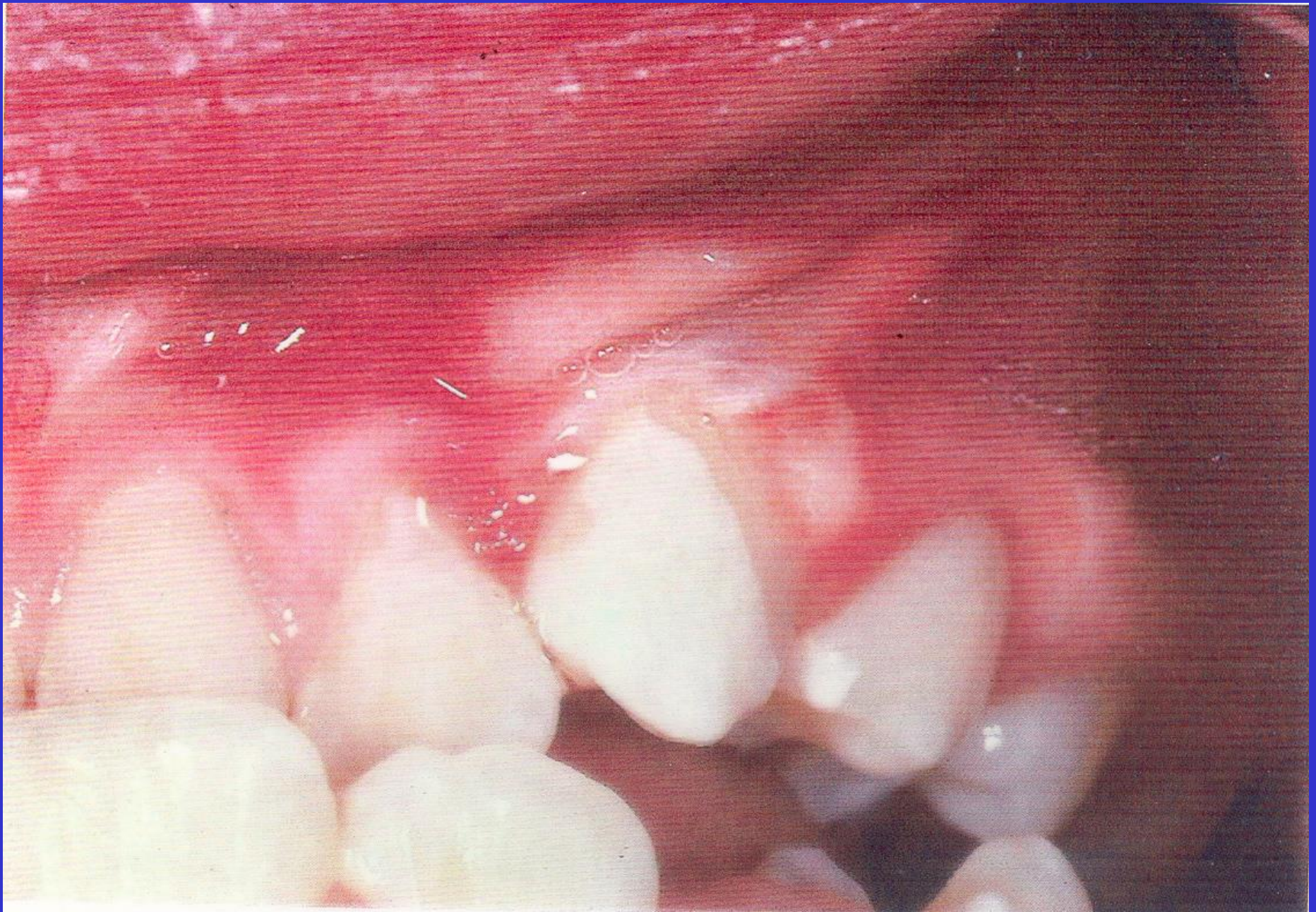


















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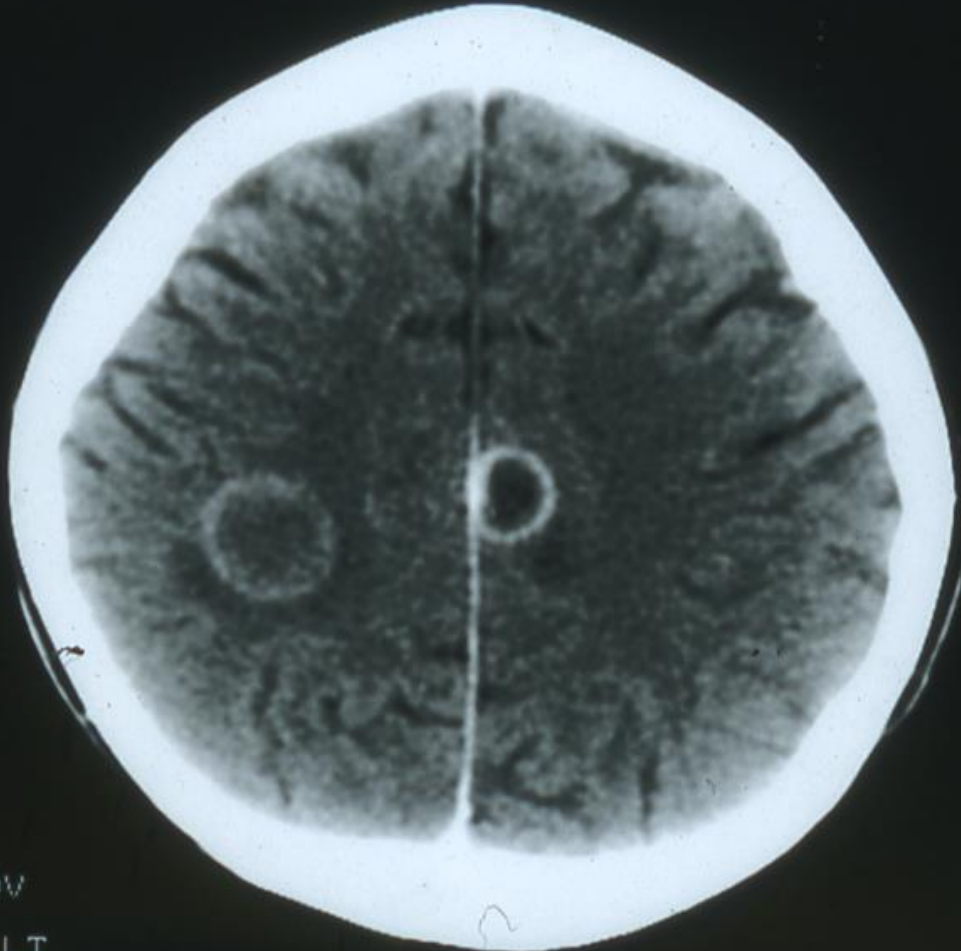
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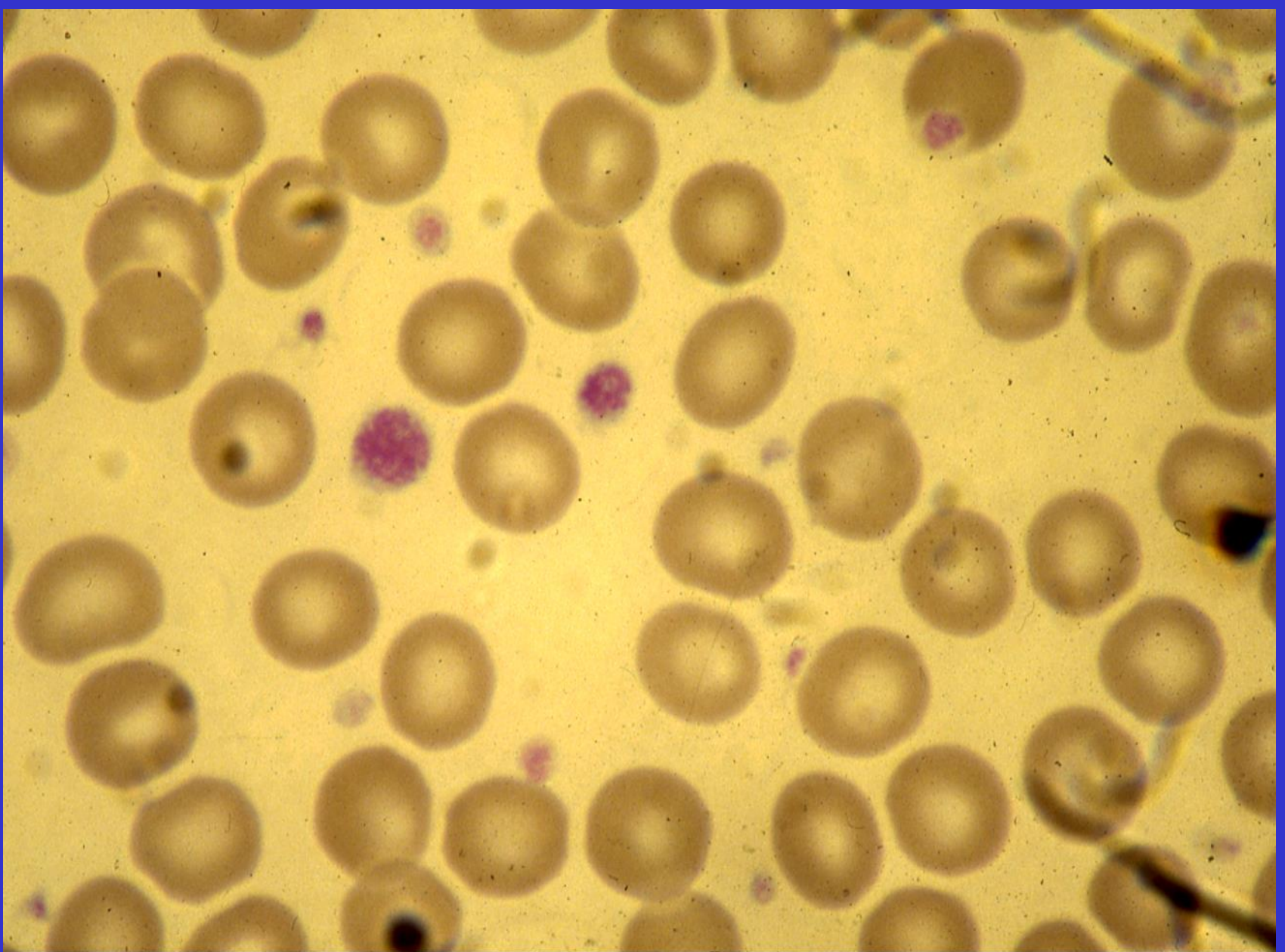


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## Laboratory features of immune thrombocytopenia

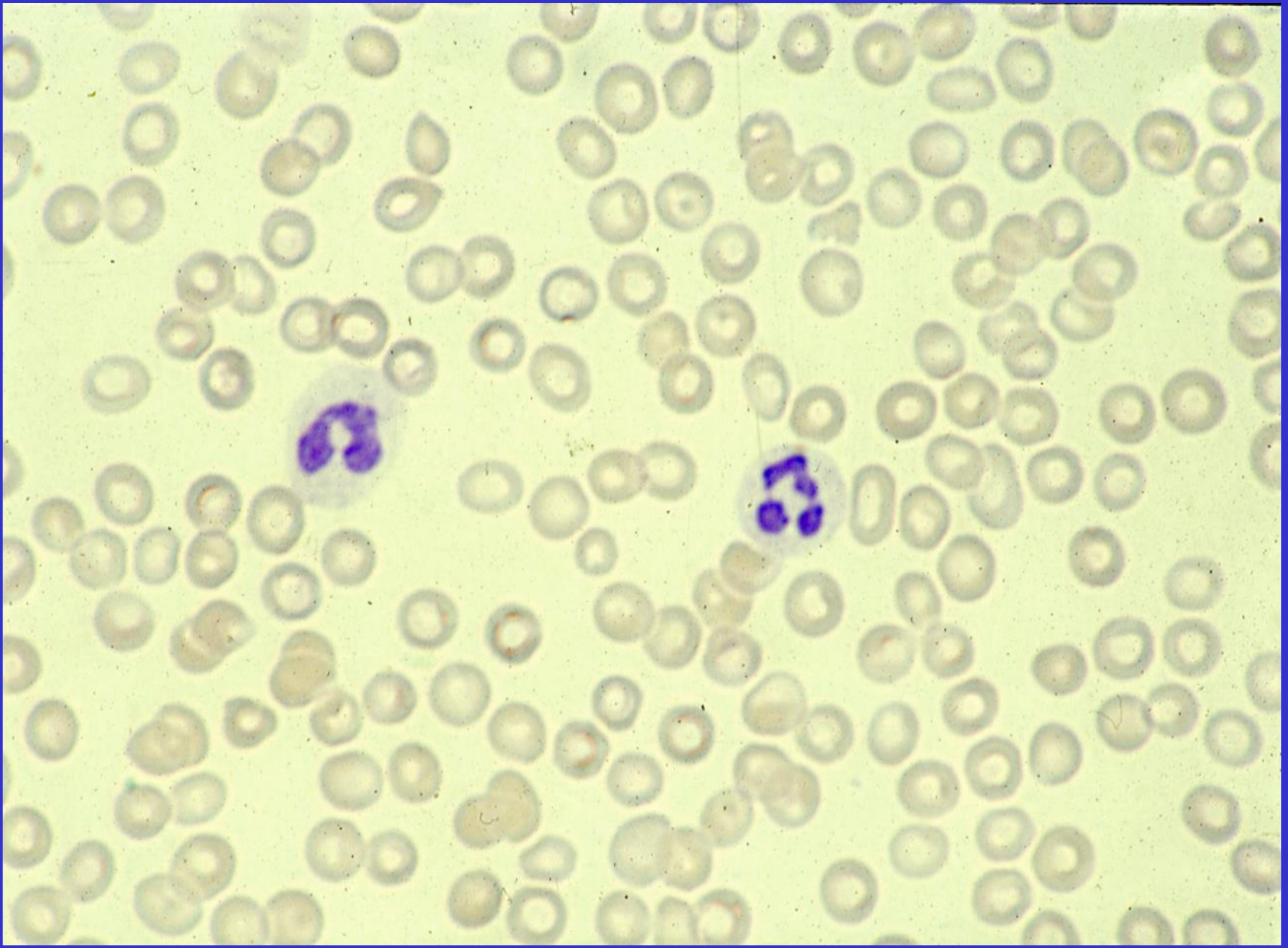
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- ❖ Thrombocytopenia with increased numbers of large platelets ( $>3\mu$ )
- ❖ Increased numbers and size of megakaryocytes.
- ❖ Reduced intravascular platelet survival.
- ❖ Elevated levels of platelet-associated IgG or IgM.



**Normal blood film.**





**Blood film from ITP patient (severe thrombocytopenia).**



# Treatment

## Acute ITP

Over 80% of patients recover without any treatment.

- Corticosteroids are widely used
- High doses of intravenous immunoglobulin (Ig) cause a rapid increase in the platelet count

## Chronic ITP

Treatment is usually not needed in patients with platelet counts above  $30-50 \times 10^9/L$  who have no significant spontaneous bleeding.

- High-dose corticosteroid therapy increases the platelet count to more than  $50 \times 10^9/L$
- Prednisolone 60 mg/day

*cont'd...*

- Splenectomy
- Second-line treatment
- Azathioprine, cyclophosphamide, danazol, dapsone, cyclosporine A, mycophenolate mofetil and rituximab have all been used, particularly in patients who fail to respond to splenectomy.
- High dose of intravenous Ig (e.g. 1 g/kg/day for 2 days) has also been found to increase the platelet count to greater than  $50 \times 10^9/L$  in 80% of patients with chronic ITP.

# Thrombocytopenia as a result of drugs or toxins

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- Bone marrow suppression
- Predictable (dose-related)  
ionizing radiation, cytotoxic drugs, ethanol
- Occasional
- chloramphenicol, co-trimoxazole, idoxuridine, penicillamine, organic arsenicals, benzene, etc.
- Immune mechanisms (proven or probable)
- Analgesics, anti-inflammatory drugs, gold salts
- Antimicrobials  
penicillins, sulphonamides, trimethoprim, rifampicin



# Thrombocytopenia as a result of drugs or toxins

(Continued...)

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- sedatives, anticonvulsants
  - diazepam, sodium valproate, carbamazepine
- Diuretics
  - acetazolamide, chlorothiazides, furosemide
- Antidiabetics
  - chlorpropamide, tolbutamide
- Others
  - digitoxin, heparin, methyldopa, oxyprenolol, quinine, quinidine
- Platelet aggregation
  - Ristocetin, heparin

# Thrombotic thrombocytopenic purpura (TTP)

- In healthy individuals a VWF-cleaving protease (ADAMTS 13) cleaves the Tyr 842-Met 843 peptide bond in VWF to produce the characteristic multimer profile. In the absence of the protease, ultra-large VWF multimers are released that lead to platelet aggregation and the disease known as ‘thrombotic thrombocytopenic purpura’ (TTP).
- This is a serious illness characterized by widespread arteriolar platelet thrombi leading to fragmentation of red cells, thrombocytopenia, neurological symptoms and renal impairment.

## **TTP & HUS**

- **Clinical Features**

Fever, Thrombocytopenic purpura, Haemolytic Anaemia, Neurological symptoms & renal Dysfunction.

- **Association with other conditions**

- **Genetic predisposition**

- **Infections - Bacterial, E-coll type 0157, shigella dysenteriae serotype I, and viral infection.**

- **Hypersensitivity**

### **Pregnancy:**

- **Oral contraceptives**

- **Auto Immune Disease**

- **SLE**

- **Rheumatoid, Arthritis**

- **Rheumatoid, Spondylitis**

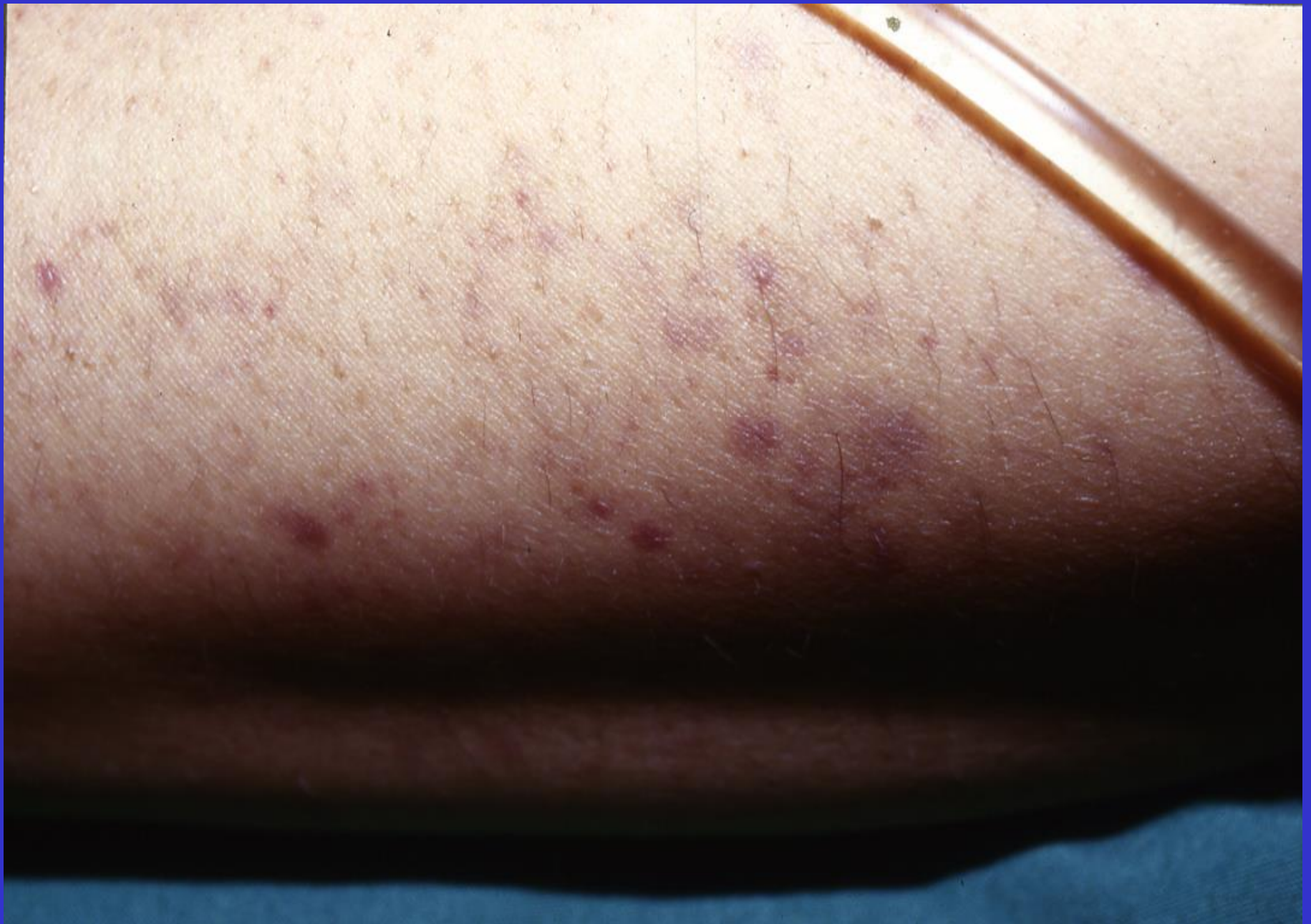
- **Polyarthritis Nodosa**

- **Sjorgen's Syndrome**

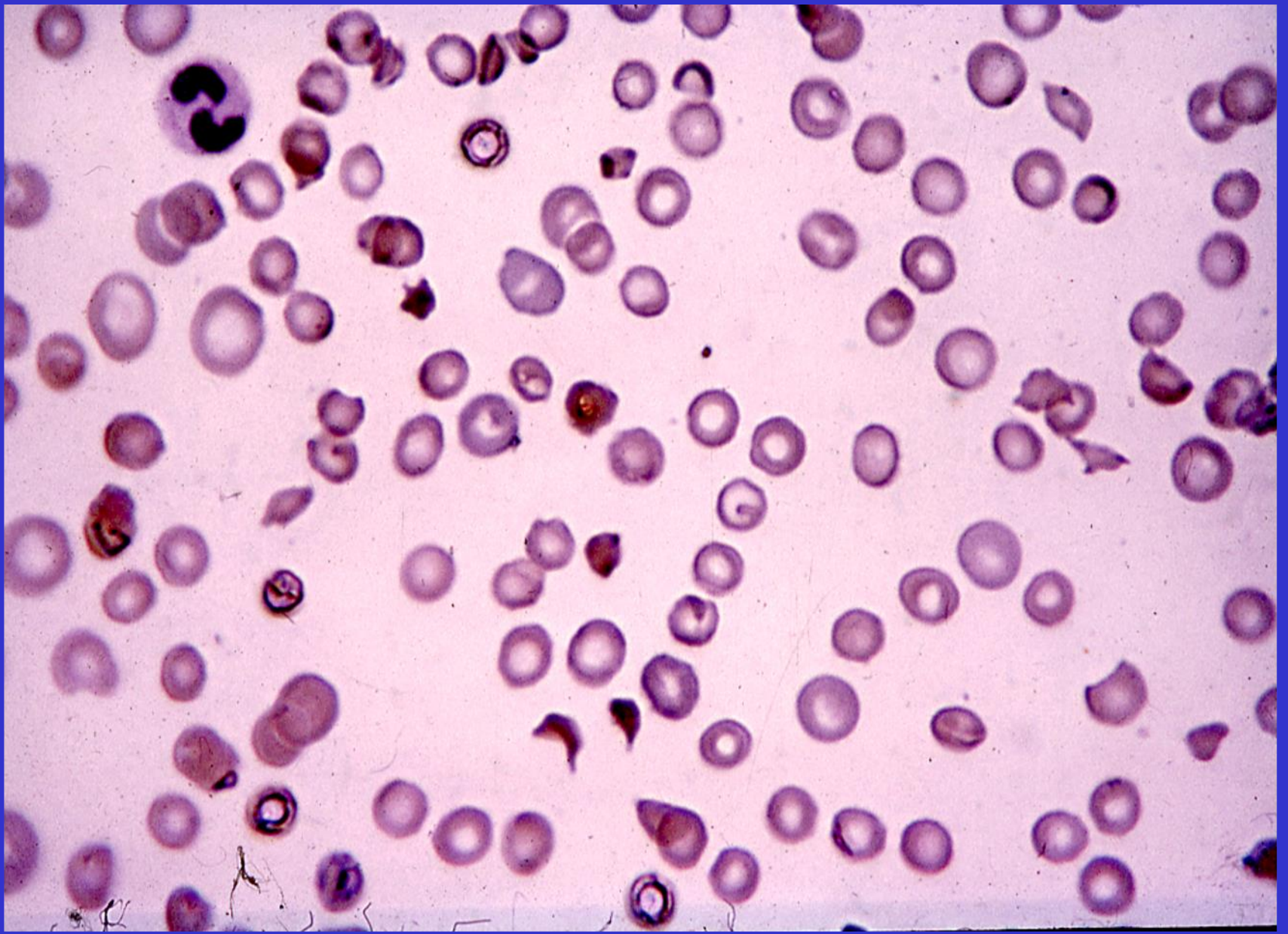


## *TTP - HUS Associated with Chemotherapy*

- **Mitomycin**
- **Cisplatinum**
- **Bleomycin**
- **Vindesine**
- **Vinblasine**
- **Doxorubicin**
- **Vincristine + Asparaginase + Prednisone**
- **Cyclosporin**

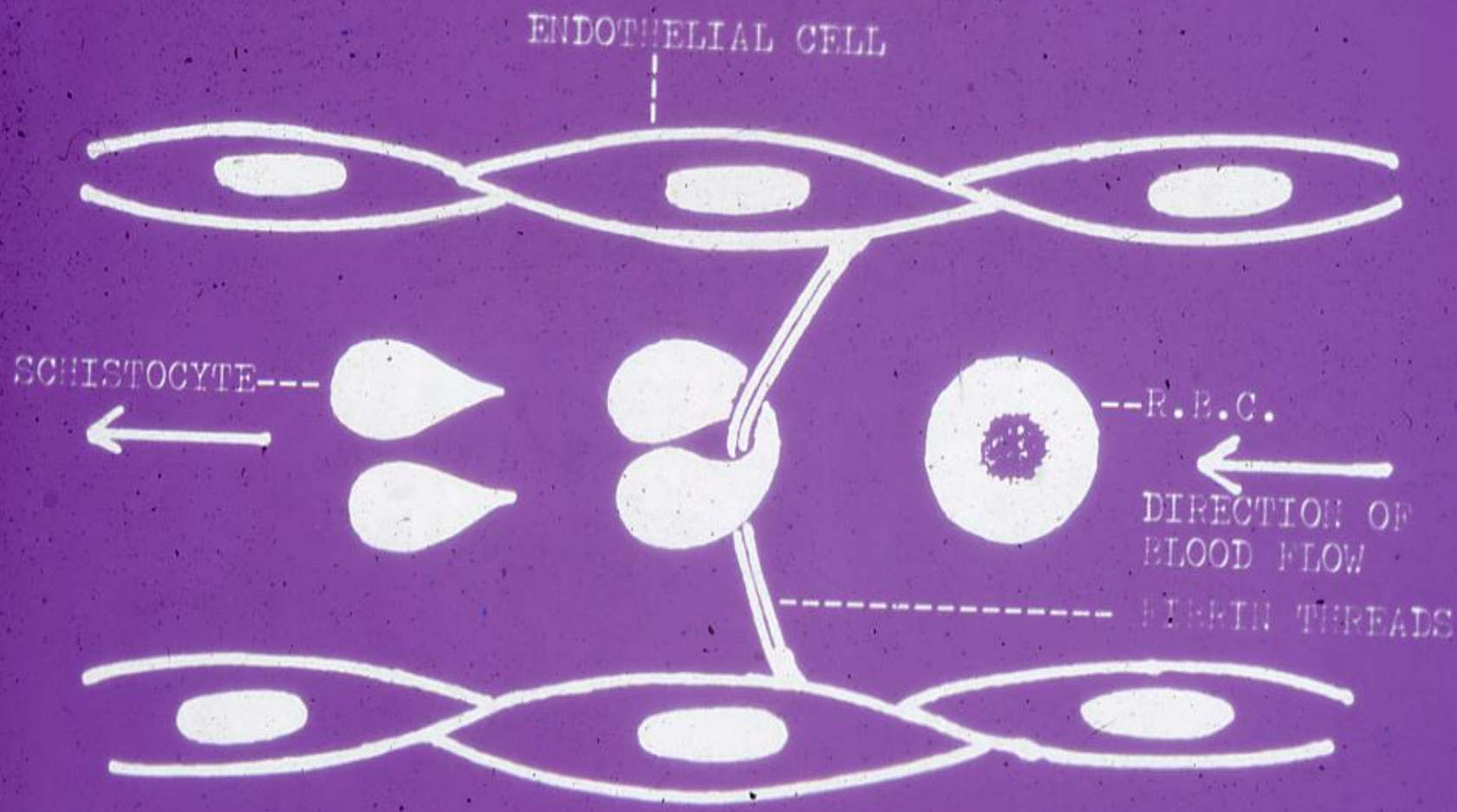






**Blood film from TT patient (showing many schistocytes).**





# BLOOD COUNT FILM

## LOW PLATELET COUNT

- 1-BONE MARROW EXAMINATION
- 2-PLATELET ANTIBODIES
- 3-SCREEN TESTS FOR DIC

## NORMAL PLATELET COUNT

- 1-BLEEDING TIME
- 2-PLATELET AGGREGATION  
STUDIES WITH ADP,ADRENALIN,  
COLLAGEN AND RISTOCETIN
- 3 -OTHER SPECIAL PLATELET TESTS  
eg. ADHENSIONSTUDIES,NUCLEOTIDE,  
POOL MEASUREMENT
- 4- FACTOR VIII CLOTTING ASSAY  
vWF ASSAY  
vWF ANTIGEN ASSAY

# Platelet transfusions

- It is often possible to raise the platelet count temporarily by platelet transfusions.
- The main indication for platelet transfusion is severe haemorrhage caused by:
  - (i) Thrombocytopenia due to diminished platelet production or DIC; or
  - (ii) Abnormal platelet function.



*cont'd...*

- Transfusion may also be indicated in a patient with thrombocytopenia or defective platelet function prior to surgery.
- Another indication for platelet transfusion is thrombocytopenia (platelets  $<50 \times 10^9/L$ ) in patients receiving massive blood transfusions.
- Platelet counts need only be maintained above  $10-20 \times 10^9/L$ , since severe bleeding is rare above this level.

A tropical beach scene at sunset. The sky is a mix of deep blue, purple, and orange, with large, dark clouds. Several palm trees are silhouetted against the sky. The ocean is visible in the background, and the foreground shows a sandy beach. The text "Thank you !!!" is written in a yellow, cursive font across the bottom of the image.

*Thank you !!!*